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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Basic Neuroscience Research

MR Imaging in Conscious Monkeys

Functional magnetic resonance imaging (fMRI) has developed into a powerful tool for measuring and comparing biological processes, both in human and nonhuman subjects. Preclinical fMRI studies have several advantages; for example, they allow repeated measures in the same subjects, they can be combined with invasive measures such as electrophysiology or neurochemistry, and they can be used to evaluate the effects of novel pharmacotherapies. One disadvantage of preclinical fMRI to date has been the necessity to conduct the scanning in anesthetized animals to eliminate movement artifacts, which can distort the images. Another drawback for using anesthetized animals is that the signals measured by fMRI are suppressed by the sedative actions of the drugs. Dr. Leonard Howell and his colleagues at Emory University and the Yerkes National Primate Research Center have developed an innovative apparatus and a behavioral training method for conducting fMRI studies in conscious monkeys and evaluating the effects of cocaine administration. The apparatus consists of a PVC cylindrical frame that encases a silicone rubber mold custom fitted for each animal to minimize head movement. To minimize stress to the animals, all subjects were gradually habituated to all of the procedures necessary for the imaging studies over the course of several months. This included exposing the animals to the sights and sounds of the imaging procedures by using a mock fMRI chamber. After the animals had acclimated to the procedure, they were scanned while physiological measures of stress such as heart rate, blood pressure, and plasma cortisol levels were collected. The results showed that these physiological measures were stable both within and across sessions and did not differ from those measures when the animals were immobilized with standard primate handling procedures. Subject motion and blood oxygenation level dependent (BOLD) fMRI measures were then evaluated by scanning the animals under three conditions: 1) the absence of any stimulation; 2) presentation of a visual stimulus; and 3) administration of 0.3 mg/kg of i.v. cocaine. Dr. Howell and his colleagues concluded that these training and scanning methods combined with their newly-developed head-restraint apparatus were effective for fMR imaging in conscious animals and for evaluating the effects of psychoactive drugs. Murnane KS, Howell LL. Development of an apparatus and methodology for conducting functional magnetic resonance imaging (fMRI) with pharmacological stimuli in conscious rhesus monkeys. *J Neurosci Meth.* 2010; 191: 11-20.

Neuropathic Pain

The use of opioids in treating chronic neuropathic pain, by activating mu opioid receptors (MORs), is associated with undesirable side effects and the development of opioid-mediated antinociceptive tolerance. Dr. Victor Hruby

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and collaborators at the University of Arizona have recognized that chronic opioid exposure in animals leads to release of the neuropeptide substance P, activating the neurokinin receptor (NK1). These considerations have produced a research program to develop bifunctional peptides exhibiting both MOR agonism and NK1 antagonism. A recent publication describes the in-vivo properties of one such octapeptide TY005 given to uninjured and spinal nerve-ligated (SNL) rats. Acute intrathecal injections of TY005 in uninjured rats produced dose-dependent antinociception (paw withdrawal latency), without motor impairment (rotarod testing), and blocked by the antagonists naloxone, beta-FNA, and naltrindole. After establishing the SNL injury in rats, a single intrathecal TY005 injection produced significant reversal of tactile allodynia and thermal hyperalgesia, as compared to a test group of rats receiving morphine, and to a control group measured pre- and post-SNL. Similar results were also found for acute intravenous TY005 injections. Chronic results were obtained by administration of i.t morphine or TY005 to spinal nerve-ligated or unligated (sham) rats twice daily for eleven days, followed by a washout period on days 12-15, and a rechallenge on day 15. While morphine showed a decrease in antihyperalgesic efficacy over this time frame, TY005 retained its antiallodynic and antihyperalgesic efficacy. The extent of TY005 availability across the blood brain barrier, and the metabolic stability of the TY005 peptide will be further examined, in considering this group of peptides as potential therapeutic agents. This work was funded by grant DA013449. Largent-Milnes TM, Yamamoto T, Nair P, Hruby VJ, Lai J, Porreca F, Vanderah TW. Spinal or Systemic TY005, a Peptide Opioid Agonist/Neurokinin 1 Antagonist, Attenuates Pain with Reduced Tolerance. *British Journal of Pharmacology*. 2010 November; 161(5); 986-1001.

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THC Exposure Leads to Myeloid-Derived Suppressor Cell Expansion Demonstrating Immunosuppressive Properties

Hegde and colleagues show that administration of THC in mice leads to rapid and massive expansion of CD11b+Gr-1+ myeloid-derived suppressor cells (MDSC) exhibiting potent immunosuppressive properties both in vitro and in vivo. MDSC belong to a suppressor cell population capable of reducing anti-tumor and inflammatory immune responses. It has been known that cannabinoids have immunosuppressive and anti-inflammatory properties; however what has not been elucidated are the effects of THC on MDSC. Na•ve mice exposed to a single dose of THC, as low as 5-10 mg/kg, presented with a significant increase in MDSC. Upon stimulation in vitro these cells cause an inhibition in the proliferation of T cells as well as antigen-specific stimuli. In vivo, MDSC leads to an inhibition of conA-induced T-cell-mediated liver inflammation. The authors show that the effect of THC is mediated directly through activation of both CB1 and CB2, as select receptor antagonists could partially block MDSC induction by THC, however CB1 and CB2 KO mice showed significant reduction of MDSC compared to WT controls confirming the involvement of both receptors. It is also believed that THC induces the proliferation of migrated MDSC in the periphery as evidence by significant proportion of actively proliferating MDSC in the peritoneum of THC injected mice. In light of the work presented in this manuscript as well as other studies, at pharmacological or recreational doses, THC may induce MDSC and lead to immunosuppression. Though more research in this area is needed, it is suggestive that induction of MDSC by cannabinoids may make an individual more susceptible to certain types of cancer, particularly those that do not express cannabinoid receptors. Hegde V, Nagarkatti M, Nagarkatti PS. Cannabinoid receptor activation leads to massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties. *Eur J Immunol*. 2010; 40: 3358-3371.

Spinal Cord MOR/KOR Heterodimers Represent A Unique Pharmacological Target for Female-Specific Pain Control

Sexually dimorphic nociception and opioid antinociception is very pervasive but poorly understood. Earlier, these researchers had demonstrated that spinal morphine antinociception in females, but not in males, requires the concomitant activation of spinal μ -opioid receptor (MOR) and κ -opioid receptor (KOR), suggesting an interrelationship between MOR and KOR in females, but not in males. In this manuscript, these researchers show that expression of a MOR/KOR heterodimer is vastly more prevalent in the spinal cord of proestrous vs. diestrous females and vs. males. Cross-linking experiments in combination with in vivo pharmacological analyses indicate that heterodimeric MOR/KOR utilizes spinal dynorphin 1-17 as a substrate and is likely to be the molecular transducer for the female-specific KOR component of spinal morphine antinociception. The activation of KOR within the heterodimeric MOR/KOR provides a mechanism for recruiting spinal KOR-mediated antinociception without activating the concomitant pronociceptive functions that monomeric KOR also subserves. Spinal cord MOR/KOR heterodimers represent a unique pharmacological target for female-specific pain control. Chakrabarti S, Liu NJ, Gintzler AR. Formation of μ -/ κ -opioid receptor heterodimer is sex-dependent and mediates female-specific opioid analgesia. *Proc Natl Acad Sci USA*. 2010 Nov 16; 107(46): 20115-20119.

Lipidomic Metabolism Analysis of the Endogenous Cannabinoid Anandamide (N-arachidonyl-ethanolamide)

Elucidation of pathways involved with lipid metabolism has been limited by analytical challenges associated with detection and structure identification. A discovery based mass spectrometry lipidomic approach has been applied to identify metabolites of the endogenous cannabinoid anandamide (N-arachidonyl-ethanolamide). Previously, a model system was established to show that anandamide can be recycled by cells to form new endocannabinoids suggesting recycling of the arachidonate carbon chain. The authors have hypothesized that distinct cellular pathways exist to direct anandamide-derived arachidonate chain into a specific set of metabolites, different from the metabolite pool that is comprised of non-anandamide-derived arachidonic acid. Using stable isotope encoding and liquid chromatography-mass spectrometry, the authors have identified a distinct pool of lipid metabolites derived from exogenous anandamide or arachidonic acid in RBL-2H3 cells. They have discovered that arachidonic acid -derived metabolites were primarily comprised of the eicosanoid lipid class, whereas anandamide-derived arachidonic acid, in addition to eicosanoids, was metabolized into diradylglycerols, fatty acid amides, sterols, and glycerophospholipids. From the list of anandamide metabolites of particular interest was 1-O-arachidonyl-sn-glycero-3-phosphocholine. Furthermore, the authors determined that whereas 1-O-arachidonyl-sn-glycero-3-phosphocholine may be a metabolite of anandamide, the sn-2 compound was more abundant in mouse brain tissue. Overall, the results provide a novel approach to study the metabolic fate of endocannabinoids and fatty acid-derived signaling molecules. Placzek EA, Cooper BR, Placzek AT, Chester JA, Davison VJ, and Barker EL. Lipidomic metabolism analysis of the endogenous cannabinoid anandamide (N-arachidonyl-ethanolamide). *J Pharmaceutical and Biomedical Analysis*. 2010; 53: 567-575.

FAAH Inhibitor As A Target for Drug Development

The enzyme fatty acid amide hydrolase (FAAH) catalyzes the in vivo degradation of the endocannabinoid anandamide, thus controlling its action at receptors. A novel FAAH inhibitor, AM3506, normalizes the elevated blood pressure and cardiac contractility of spontaneously hypertensive rats (SHR) without affecting these parameters in normotensive rats. These effects are due to blockade of FAAH and a corresponding rise in brain anandamide levels,

resulting in CB(1) receptor-mediated decrease in sympathetic tone. The supersensitivity of SHR to CB(1) receptor-mediated cardiovascular depression is related to increased G protein coupling of CB(1) receptors. Importantly, AM3506 does not elicit hyperglycemia and insulin resistance seen with other FAAH inhibitors or in FAAH(-/-) mice, which is related to its inability to inhibit FAAH in the liver due to rapid hepatic uptake and metabolism. This unique activity profile offers improved therapeutic value in hypertension. Godlewski G, Alapafuja SO, Batkai S, Nikas SP, Cinar R, Offertaler L, Osei-Hyiaman D, Liu J, Mukhopadhyay B, Harvey-White J, Tam J, Pacak K, Blankman JL, Cravatt BF, Makriyannis A, Kunos G. Inhibitor of fatty acid amide hydrolase normalizes cardiovascular function in hypertension without adverse metabolic effects. *Chem Biol.* 2010 Nov 24; 17(11): 1256-1266.

Variation in Nicotinic Acetylcholine Receptor Genes is Associated with Multiple Substance Dependence Phenotypes

There is shared genetic risk for dependence on multiple substances, and the nicotinic receptor gene cluster on chromosome 15 harbors multiple genetic polymorphisms that associate to this risk. Dr. Gelernter and colleagues reported the results of an association study with 21 single nucleotide polymorphisms (SNPs) genotyped across the CHRNA5, CHRNB4, and CHRNA3 loci on chromosome 15q25.1. The sample consisted of a discovery set (N=1858) of European-American and African-American (AA) families, ascertained on the basis of a sibling pair with cocaine and/or opioid dependence, and a case-control replication sample (N=3388) collected for association studies of alcohol, cocaine, and opioid dependence. The research team tested the SNPs for association with lifetime cocaine, opioid, nicotine, and alcohol dependence (AD). Several previous findings were replicated, including associations between rs16969968 and nicotine dependence (P=0.002) and cocaine dependence (CD) (P=0.02), with opposite risk alleles for each substance. They observed these associations in AAs, which is a novel finding. The strongest association signal in either sample was between rs684513 in CHRNA5 and cocaine dependence (OR=1.43, P=0.0004) in the AA replication set. The research team also observed two SNPs associated with alcohol dependence, that is, rs615470 in CHRNA5 (OR=0.77, P=0.0006) and rs578776 (OR=0.78, P=0.001). The associations between CD and rs684513, AD and rs615470, and AD and rs578776 remained significant after a permutation-based correction for multiple testing. These data reinforce the importance of variation in the chromosome 15 nicotinic receptor subunit gene cluster for risk of dependence on multiple substances, although the direction of the effects may vary across substances. Sherva R, Kranzler HR, Yu Y, Logue MW, Poling J, Arias AJ, Anton RF, Oslin D, Farrer LA, Gelernter J. Variation in nicotinic acetylcholine receptor genes is associated with multiple substance dependence phenotypes. *Neuropsychopharmacology.* 2010 Aug; 35(9): 1921-1931.

Cortico-Thalamic Connectivity is Vulnerable to Nicotine Exposure During Early Postnatal Development Through $\alpha 4/\beta 2/\alpha 5$ Nicotinic Acetylcholine Receptors

Previous work suggests that exposure to tobacco smoke during pregnancy is associated with altered processing of sensory stimuli in humans. Studies in rodents suggest that this deficit is produced by exposure to nicotine, the major psychoactive component in tobacco smoke, during a critical period corresponding to the third trimester of gestation in humans. Nicotine appears to alter the development of corticothalamic neurons and impairs a behavioral task dependent on auditory processing. Dr. Picciotto explored the mechanisms by which nicotine alters somatosensory processing using a passive avoidance task. Dr. Picciotto and her colleagues show that exposure of mouse pups to nicotine from birth to weaning of day 21 is the critical period for inducing hypersensitive passive avoidance, as show as delay of entering a chamber

where the mouse had received shock 3 days earlier. Using transgenic mice, Dr. Piciotto and her colleagues suggest that the development of a hypersensitive passive avoidance response is dependent upon the expression of the nicotinic receptor $\beta 2$ subunit in corticothalamic neurons. The $\beta 2$ subunit in these corticothalamic neurons combines with $\alpha 4$ and $\alpha 5$ subunits to preferentially form $(\alpha 4)_2(\beta 2)_2\alpha 5$ nicotinic receptors in these neurons. Consistent with the theory that desensitization of $(\alpha 4)_2(\beta 2)_2\alpha 5$ nicotinic receptor by chronic nicotine mediates hypersensitive passive avoidance is the observation that the constitutive knockout of $\alpha 5$ produces a hypersensitive passive avoidance response. These results show the behavioral teratogenic consequences of nicotine exposure during a period in the mouse that corresponds third trimester of pregnancy in humans when the cortico-thalamic circuitry is being refined. This study may inform the debate about the timing and the best type of smoking cessation therapy for pregnant smokers. Heath CJ, King SL, Gotti C, Marks MJ, Piciotto MR. Cortico-thalamic connectivity is vulnerable to nicotine exposure during early postnatal development through $\alpha 4/\beta 2/\alpha 5$ nicotinic acetylcholine receptors. *Neuropsychopharmacology*. 2010; 35(12): 2324-2338.

AChR $\alpha 5$ Subunit Variant Associated With Risk for Nicotine Dependence and Lung Cancer Reduces $(\alpha 4)_2(\beta 2)_2\alpha 5$ AChRs Function

Genetic studies have identified a variant in the coding region of the $\alpha 5$ AChR associated with increased risk for the number of cigarettes smoked and lung cancer. This variant changes the amino acid at position 398 in the protein from aspartic acid to asparagines (D398N). Dr. Wade Berrettini in collaboration with Dr. Jon Lindstrom's laboratory show that D398 decreases the Ca^{++} permeability and increases acute desensitization in $(\alpha 4\beta 2)_2\alpha 5$, but not in $(\alpha 3\beta 4)_2\alpha 5$ or $(\alpha 3\beta 2)_2\alpha 5$ AChR. 60% of $(\alpha 4\beta 2)_2\alpha 5$ nicotinic receptors are desensitized at 0.2 μM nicotine, the typical concentration of nicotine found in smokers but concentrations as high as 10 μM nicotine have no effect on desensitization of $(\alpha 3\beta 4)_2\alpha 5$ or $(\alpha 3\beta 2)_2\alpha 5$. The authors suggest that a positive allosteric modulator of $(\alpha 4\beta 2)_2\alpha 5$ may be useful in treating nicotine dependence which would restore the ability of acetylcholine and nicotine to modulate presynaptic release through $(\alpha 4\beta 2)_2\alpha 5$ located on the presynaptic terminals of neurons. Kuryatov A, Berrettini WH, Lindstrom JM. Acetylcholine Receptor (AChR) $\{\alpha\}5$ Subunit Variant Associated with Risk for Nicotine Dependence and Lung Cancer Reduces $(\{\alpha\}4\{\beta\}2)_2\{\alpha\}5$ AChR Function. *Mol Pharmacol*. 2010 Sep 29. [Epub ahead of print]

Cell Type-specific Loss of BDNF Signaling Mimics Optogenetic Control of Cocaine Reward

There are two types of dopamine receptors, DRD1 and DRD2 that are expressed in two distinct neuronal pathways. DRD1 dopamine receptors are expressed in neurons that project from the striatum to the substantia nigra, known as the direct pathway; DRD2 receptors are expressed in neurons that project from the striatum to the pallidum, known as the indirect pathway. Cocaine activates both receptors by blocking the uptake of dopamine. Dr. Eric Nestler and his colleagues, using a technique called optogenetic stimulation, show that stimulating DRD1 expressing neurons with blue light increases the rewarding properties of cocaine while stimulating DRD2 neurons with blue light inhibits the rewarding properties of cocaine. The effect is in part mediated by the neurotrophic factor BDNF. Optogenetic stimulation of DRD1 receptor expressing neurons blocks downstream targets of BDNF. Nestler and his colleagues in the paper show that blocking the effects of BDNF in DRD1 receptor expressing neuron, by selectively deleting the BDNF receptor, increases the rewarding properties of cocaine. In contrast, optogenetic stimulation of DRD2 expressing neurons does not block the downstream targets of BDNF, which in the case of DRD2 neuron would lead to a decrease in

the rewarding effects of cocaine. Thus, when both DRD1 and DRD2 neurons are activated by cocaine the overwhelming response is reward. By selectively stimulating or inhibiting these pathways, new therapies for the treatment of addiction may be found. Lobo MK, Covington HE 3rd, Chaudhury D, Friedman AK, Sun H, Damez-Werno D, Dietz DM, Zaman S, Koo JW, Kennedy PJ, Mouzon E, Mogri M, Neve RL, Deisseroth K, Han MH, Nestler EJ. Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science*. 2010; 330(6002): 385-390.

Narp Regulates Homeostatic Scaling of Excitatory Synapses on Parvalbumin-expressing Interneurons

It has been well known that changes of synaptic strength, namely long term potentiation (LTP) or long-term depression (LDP), underlie the major mechanism for neural plasticity. This neural plasticity is in turn the basis for learning and memory. Learning and memory are critically involved in short and long term adaptations to drugs of abuse. For synaptic changes to function for a specific learning task, the background homeostatic dynamics and long term stability of the neural circuits has to be maintained within an optimal range to prevent occlusion of further increase or decrease of neural activity. In other words, a homeostatic mechanism, termed homeostatic scaling must be in place to adjust the relative strength of all neuron's excitatory synapses up or down to stabilize firing in response to changes in average post-synaptic activity. How homeostatic stability is regulated in neural circuitry has not been well understood. One hypothesis is that homeostatic scaling of excitatory scaling occurs through mechanisms that regulate glutamate receptor trafficking. A research team led by Paul Worley, a NIDA funded researcher at Johns Hopkins University, reports that a secreted synaptic protein, neuronal activity-regulated pentraxin (Narp), regulates homeostatic adaptations of circuit activity by enhancing the strength of excitatory synapses on the excitatory parvalbumin-expressing interneurons, concomitantly increasing their network-driven firing rate. The increased firing of these parvalbumin-expressing interneurons causes the release of the inhibitory neurotransmitter, GABA, that inhibits the overall excitability of the network. Narp is an immediate early gene that is dynamically regulated by synaptic activity. The team reports that Narp was highly enriched at excitatory synapses that are found specifically on parvalbumin-expressing interneurons. Its expression was dynamically regulated by network activity. First, the accumulation of Narp at these synapses resulted from its secretion from presynaptic excitatory neurons and required the presence of perineuronal nets around parvalbumin-expressing interneurons. Second, the accumulation of Narp increased the strength of excitatory synapses on parvalbumin-expressing interneurons, both in culture and in the acute hippocampal slice preparation. Narp increases the strength of excitatory synapses through regulating the expression of GluR4-containing AMPARs in an activity-dependent manner. Furthermore, in neurological testing, mice lacking Narp showed a marked increase in sensitivity to kindling-induced seizure. Together, these results indicate that Narp contributes to homeostatic plasticity of interneurons and suggest that Narp is important for the activity-dependent recruitment of parvalbumin-expressing interneuron mediated inhibition. Understanding the role that homeostatic scaling plays in the nervous system may lead to a better understanding of the etiology of brain disease in which parvalbumin-expressing interneurons have been implicated. Chang MC, Park JM, Pelkey KA, Grabenstatter HL, Xu D, Linden DJ, Sutula TP, McBain CJ and Worley PF. Narp regulates homeostatic scaling of excitatory synapses on parvalbumin-expressing interneurons. *Nature Neuroscience*. 2010; 13: 1090 - 1097.

Neuroanatomical Substrate in the Nucleus Accumbens May Contribute to Behavioral Sex Differences in Reward and Addiction

Forlano and Woolley evaluated the pre- and postsynaptic measures (size, local

density, and location within the nucleus accumbens) of dendritic spines present on glutamatergic neurons as well as the densities and distributions of tyrosine hydroxylase, PSD-95, and the vesicular glutamate transporter in male and proestrous female rats. Tyrosine hydroxylase and the vesicular glutamate transporter did not differ between the sexes. However, females had more glutamatergic input onto medium spiny neurons on the distal dendrites, the major site of dopaminergic and glutamatergic convergence. Females also had a greater proportion of large spines than the males. There were sex differences in both core and shell of the accumbens, but the differences were greater in the core. They also found that the females exhibited greater spine head size and a greater PSD-95 volume, suggesting that medium spiny neurons in females may have more strong excitatory synapses than males. This difference may reflect a disparity in synaptic plasticity between the sexes and may predict greater susceptibility to psychostimulants in females. Forlano P and Woolley CS. Quantitative analysis of pre- and postsynaptic sex differences in the nucleus accumbens. *J Comp Neurol.* 2010; 518: 1330-1348.

Global and Local fMRI Signals Driven by Neurons Defined Optogenetically by Type and Wiring

Despite a rapidly-growing scientific and clinical brain imaging literature based on functional magnetic resonance imaging (fMRI) using blood oxygenation level-dependent (BOLD) signals, it remains controversial whether BOLD signals in a particular region can be caused by activation of local excitatory neurons. This difficult question is central to the interpretation and utility of BOLD, with major significance for fMRI studies in basic drug abuse research and clinical applications. Using a novel integrated technology unifying optogenetic control of inputs with high-field fMRI signal readouts, Dr. Karl Deisseroth's laboratory at the Stanford University and his collaborators from various universities show that specific stimulation of local CaMKII α -expressing excitatory neurons, either in the neocortex or thalamus, elicits positive BOLD signals at the stimulus location with classical kinetics. They also show that optogenetic fMRI (ofMRI) allows visualization of the causal effects of specific cell types defined not only by genetic identity and cell body location, but also by axonal projection target. Finally, they show that ofMRI within the living and intact mammalian brain reveals BOLD signals in downstream targets distant from the stimulus, indicating that this approach can be used to map the global effects of controlling a local cell population. In this respect, unlike both conventional fMRI studies based on correlations and fMRI with electrical stimulation that will also directly drive afferent and nearby axons, this ofMRI approach provides causal information about the global circuits recruited by defined local neuronal activity patterns. Together these findings provide an empirical foundation for the widely-used fMRI BOLD signal, and the features of ofMRI define a potent tool that may be suitable for functional circuit analysis as well as global phenotyping of dysfunctional circuitry. Lee JH, Durand R, Gradinaru V, Zhang F, Goshen I, Kim DS, Fenno LE, Ramakrishnan C, Deisseroth K. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. *Nature.* 2010 June 10; 465: 788-792.

Activation of Calcium/Calmodulin-Dependent Protein Kinase II α in the Striatum by the Heteromeric D1-D2 Dopamine Receptor Complex

Synaptic plasticity in the striatum is a key mechanism that underlies processes such as reward related incentive learning and behavioral habit formation resulting from drugs of abuse. Key aspects of these functions are dependent on dopamine transmission as well as activation of calcium/calmodulin-dependent protein kinase II α (CaMKII α). In this study, Dr. Susan George of University of Toronto and her colleagues examined the ability of a recently identified heteromeric complex composed of D1 and D2 dopamine receptors coupled to

Gq/11 to activate striatal CaMKII α . Using the dopaminergic agonist SKF83959, which selectively activates the D1-D2 complex, they demonstrated phosphorylation of CaMKII α at threonine 286, both in heterologous cells and in the murine striatum *in vivo*. Phosphorylation of CaMKII α by activation of the receptor complex required concurrent agonism of both D1 and D2 receptors and was independent of receptor pathways that modulated adenylyl cyclase. The identification of this novel mechanism by which dopamine may modulate synaptic plasticity has implications for our understanding of striatal-mediated reward and motor function, as well as neuronal disorders in which striatal dopaminergic neurotransmission is involved. Ng J, Rashid AJ, So CH, O'Dowd BF, George SR. Activation of calcium/ calmodulin-dependent protein kinase II α in the striatum by the heteromeric D1-D2 dopamine receptor complex. *Neuroscience*. 2010; 165: 535-541.

Morphometric Differences in Recently Abstinent Methamphetamine-Dependent Individuals

A study using magnetic resonance imaging of the brain and voxel-based morphometry found that abstinent methamphetamine (MA)-dependent individuals (n=61) had less gray matter density relative to controls (n=44) in bilateral insula and left middle frontal gyrus. Impulsivity, measured by a delay discounting task, was higher in the MA group and, within all subjects, impulsivity was positively correlated with gray matter density in posterior cingulate cortex and ventral striatum, and negatively correlated in left superior frontal gyrus. Length of abstinence from MA was associated with greater amygdalar density. Earlier age of first use of MA, in subjects who initiated use before age 21, was associated with smaller intracranial volume. The findings are consistent with: a) findings of smaller intracranial volume in alcoholism and b) findings linking reduced frontocortical gray matter to an aversion to delaying gratification (Bjork et al., 2009, *Biol Psychiatry* 65(8):710-3), to underscore deviant neuromaturation as a risk factor for addiction. Further, this finding offers several putative mechanisms including neural adaptations due to chronic drug abuse, neuro-inflammation, and dopaminergic and serotonergic neurotoxicity. Schwartz DL, Mitchell AD, Lahna DL, Luber HS, Huckans MS, Mitchell SH, Hoffman WF. Global and local morphometric differences in recently abstinent methamphetamine-dependent individuals. *Neuroimage*. 2010 May 1;50(4): 1392-1401.

The Hypocretin System Regulates Motivation to Self-Administer Cocaine, but not Cocaine Consumption, via Actions on the Mesolimbic Dopamine System

These studies examined the extent to which hypocretin neurotransmission regulates behavioral and neurochemical responses to cocaine, and behavioral responses to food reinforcement. Rats were tested under operant fixed-ratio 1 (FR1, to assess consumption), discrete trials (DT, to assess motivation because access to cocaine is restricted to 3 trials/hr), progressive-ratio (PR, to assess motivation), or threshold (to assess consumption early in the trials, and to assess motivation later in the trials as the dose of cocaine is reduced every 10 min) self-administration procedures to assess whether the hypocretin-1 receptor antagonist, SB-334867, reduces cocaine consumption and/or motivation to self-administer cocaine. When SB-334867 was administered peripherally or within the ventral tegmental area, it reduced the motivation to self-administer cocaine and attenuated cocaine-induced enhancement of dopamine signaling (assessed by *in vivo* microdialysis and voltammetry in rats) within the nucleus accumbens core. SB-334867 also reduced the motivation to self-administer sucrose in food-sated but not food-restricted rats. Hypocretin knockout mice displayed reduced baseline dopamine signaling and reduced dopamine responses to cocaine (assessed by voltammetry). Combined, these studies suggest that hypocretin neurotransmission participates in

reinforcement processes, likely through modulation of the mesolimbic dopamine system. The hypocretin system may provide a target for pharmacotherapies to treat cocaine addiction. España RA, Oleson EB, Locke JL, Brookshire BR, Roberts DC, Jones SR. The hypocretin-orexin system regulates cocaine self-administration via actions on the mesolimbic dopamine system. *Eur J Neurosci.* 2010 Jan; 31(2): 336-348.

Anandamide Triggers Postsynaptic Long-term Depression (LTD) in the Dentate Gyrus via a Type 1 Cannabinoid Receptor (CB1)-Independent Manner

Endocannabinoids such as anandamide largely modulate neuronal function within the central nervous system through their actions at CB1 receptors. However, accumulating evidence is showing that endocannabinoids have additional actions independent of CB1 receptors. The transient receptor potential TRPV1 is a nonselective cation channel that mediates pain sensations and is commonly activated by a wide variety of exogenous and endogenous, physical and chemical stimuli. Although TRPV1 receptors are mainly found in nociceptive neurons of the peripheral nervous system, these receptors have been found in the brain, where their role is far less understood. This paper reports that TRPV1 activation suppressed excitatory transmission in rat and mouse dentate gyrus. This suppression was a result of Ca(2+)-calcineurin and clathrin-dependent internalization of AMPA-type glutamate receptors. Moreover, synaptic activation of TRPV1 triggered a form of long-term depression (TRPV1-LTD) mediated by the endocannabinoid anandamide in a type 1 cannabinoid receptor-independent manner. These findings reveal a previously unknown form of endocannabinoid-and TRPV1-mediated regulation of synaptic strength at central synapses. Chávez AE, Chiu CQ, Castillo PE. TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. *Nat Neurosci.* 2010 Dec; 13(12): 1511-1518.

Dopamine Release in the Striatum is Controlled by Alpha6 Subunit-Containing Nicotinic Acetylcholine Receptors (nAChR) that Also Require Alpha4 Subunits

Nicotinic acetylcholine receptors are multi-subunit proteins that can express in a variety of subunit conformations throughout the brain and central nervous system. In the striatum, dopamine (DA) release is governed by firing rates of midbrain DA neurons, striatal cholinergic tone, and nicotinic ACh receptors (nAChRs) on DA presynaptic terminals. It was previously shown that striatal DA neurons selectively express alpha6-containing nAChRs, and that transgenic mice expressing hypersensitive alpha6(L9'S)-containing receptors are hyperactive, travel greater distance, exhibit increased ambulatory behaviors such as walking, turning, and rearing, and show decreased pausing, hanging, drinking, and grooming. This paper now shows that these behaviors attributed to alpha6-containing nAChRs also require the expression of alpha4 subunits. Alpha6(L9'S) mice lacking alpha4 subunits displayed essentially normal behavior. In alpha6(L9'S) mice, receptor numbers are normal, but the loss of alpha4 subunits leads to fewer and less sensitive alpha6* receptors. Gain-of-function nicotine-stimulated DA release from striatal synaptosomes requires alpha4 subunits, further implicating an association between alpha6 and alpha4 subunits in alpha6(L9'S) mouse behaviors. In brain slices, burst stimulation of DA fibers elicited increased DA release relative to single action potentials selectively in alpha6(L9'S), but not in WT or alpha4 KO, mice. These results implicate a requirement for alpha4 subunits in alpha6-containing nAChR control of DA transmission, and strongly suggest that alpha4-alpha6 subunit-containing receptors are candidate drug targets for disorders involving the DA system. Drenan RM, Grady SR, Steele AD, McKinney S, Patzlaff NE, McIntosh JM, Marks MJ, Miwa JM, Lester HA. Cholinergic modulation of locomotion and striatal dopamine release is mediated by alpha6alpha4* nicotinic acetylcholine

receptors. *J Neurosci*. 2010 Jul 21; 30(29): 9877-9889.

Chronic THC Slowed AIDS Progression in Non-Human Primate Model

$\Delta(9)$ -Tetrahydro-cannabinol ($\Delta(9)$ -THC), the primary psychoactive component in marijuana, is FDA approved to ameliorate AIDS-associated wasting. Because cannabinoid receptors are expressed on cells of the immune system, this study was designed to investigate whether chronic $\Delta(9)$ -THC use impacts HIV disease progression, using a rhesus macaque model of AIDS. Chronic $\Delta(9)$ -THC administration (0.32 mg/kg im, 2 x daily) was started 28 days prior to inoculation with simian immunodeficiency virus (SIV(mac251); 100 TCID(50)/ml, iv). Immune and metabolic indicators of disease were measured during the initial 6 month asymptomatic phase of infection in rhesus macaques. SIV(mac251) inoculation resulted in measurable viral load, decreased lymphocyte CD4(+)/CD8(+) ratio, and increased CD8(+) proliferation. $\Delta(9)$ -THC treatment of SIV-infected animals produced minor to no effects in these parameters. However, chronic $\Delta(9)$ -THC administration decreased early mortality from SIV infection ($p = 0.039$), and this was associated with attenuation of plasma and CSF viral load and retention of body mass ($p = NS$). In vitro, $\Delta(9)$ -THC (10 μ m) decreased SIV (10 TCID(50)) viral replication in MT4-R5 cells. These results indicate that chronic $\Delta(9)$ -THC does not increase viral load or aggravate morbidity and may actually ameliorate SIV disease progression. The investigators speculate that reduced levels of SIV, retention of body mass, and attenuation of inflammation are likely mechanisms for $\Delta(9)$ -THC-mediated modulation of disease progression that warrant further study. Molina PE, Winsauer P, Zhang P, Walker E, Birke L, Amedee A, Stouwe CV, Troxclair D, McGoey R, Varner K, Byerley L, Lamotte L. Cannabinoid administration attenuates the progression of simian immunodeficiency virus. *AIDS Res Hum Retroviruses*. 2010 Nov. 23; [Epub ahead of print].

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Basic Behavioral Research

Prenatal Cocaine Exposure, Gender, and Adolescent Stress Response: A Prospective Longitudinal Study

Prenatal cocaine exposure is associated with alterations in arousal regulation in response to stress in young children. However, there is little research on the relation of cocaine exposure to stress reactivity in adolescence. The researchers in this study examined salivary cortisol, self-reported emotion, heart rate, and blood pressure (BP) responses to the Trier Social Stress Test (TSST) in 49 prenatally cocaine and other drug exposed teens (PCE) and 33 non-cocaine-exposed (NCE) adolescents. The results revealed higher cortisol levels for PCE adolescents before and after stress exposure than NCE adolescents. PCE girls showed an elevated anxiety response to stress (compared to NCE girls) and PCE boys showed a dampened diastolic BP response (compared to NCE boys). In addition, girls showed higher anger response and lower pre-stress systolic BP than boys. Group differences were found controlling for potential confounding variables and were not moderated by caregiver-child relationship quality (although relationship quality did predict HPA axis reactivity and anxiety). The findings suggest that prenatal drug exposure is associated with altered stress response in adolescence and that gender moderates this association. Chaplin TM, Freiburger MB, Mayes LC, Sinha R. Prenatal cocaine exposure, gender, and adolescent stress response: a prospective longitudinal study. *Neurotoxicology and Teratology*. 2010; 32: 595-604.

Adenosine A2A Receptor Antagonist Effects on Maternal Deficits Induced by Dopamine Receptor Antagonism

There is overlap in the neurobiological substrates subserving motivated behaviors that are naturalistic (e.g., maternal behaviors, affiliation or aggression, feeding and foraging) and those directed toward drug seeking and taking. Animal models are used to study mother-offspring interactions that are impaired in addiction, and choice behaviors have been measured to assess preference for drugs versus pups at various post-partum stages that are under hormonal control. Recently, Dr Joan Morrell and colleagues have investigated the role of interacting mesolimbic dopamine and brain adenosine systems, believed to have a role in the development of addiction, in early post-partum maternal motivation. Mesolimbic dopamine (DA), particularly in the nucleus accumbens, significantly regulates activational aspects of maternal responsiveness. DA antagonism and nucleus accumbens DA depletions interfere with early postpartum maternal motivation by selectively affecting most forms of active maternal behaviors, with no change in nursing behaviors. Research shows that there is functional interaction between DA D2 and adenosine A2A receptors in striatal areas, including the nucleus accumbens.

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The aim of this study was to determine if adenosine A2A receptor antagonism could reverse the effects of DA receptor antagonism on early postpartum maternal behavior. Researchers administered the adenosine A2A receptor antagonist, MSX-3 (0.25-2.0 mg/kg, IP), to test for effects on DA D2 receptor antagonist (haloperidol, 0.1 mg/kg, IP) induced changes in early postpartum female rats. The results revealed that haloperidol severely impaired the expression of active maternal components, including retrieval and grouping the pups at the nest site, pup licking, and nest building. Co-administration of MSX-3 (0.25-2.0 mg/kg, IP) with haloperidol produced a dose-related attenuation of these behavioral deficits. Furthermore, doses of MSX-3 that effectively reversed the effects of haloperidol (0.5, 1.0 mg/kg), when administered in absence of the D2 receptor blocker, did not affect maternal responding or locomotor activity. The researchers conclude that Adenosine and DA systems interact to regulate early postpartum maternal responsiveness. The results of this study may inform strategies for treating psychiatric disorders during the postpartum period, with particular emphasis in maintaining or restoring the mother-infant relationship. Pereira M, Farrar AM, Hockemeyer J, MYller CE, Salamone JD, Morrell JI. Effect of the adenosine A2A receptor antagonist MSX-3 on motivational disruptions of maternal behavior induced by dopamine antagonism in the early postpartum rat. *Psychopharmacology*. 2010 Sep 17 [Epub ahead of print].

Differences in Exploratory Behavior Between Late Pre-weanling and Adult Sprague-Dawley Rats

A number of childhood disorders are co-morbid with drug abuse. Vulnerability phenotypes have been identified and overlapping neurobiological substrates may be involved in childhood disorders such as conduct disorder, ADHD and the development of addiction. Animal behavioral models can be used to characterize features of this early developmental period and provide a platform for studying these co-morbid vulnerabilities. Behavioral investigations of late pre-weanling may provide a preclinical model for disorders initially manifested in early childhood that are characterized by dysfunctional interactions with environmental stimuli (e.g., obsessive-compulsive disorder and autism). However, there is no evidence in the literature of specific-stimulus exploration in the late pre-weanling rat. The researchers examined the behavioral responses of normal late pre-weanling (PND 18-19) and adult rats when presented with exemplars of categorically-varied stimuli, including inanimate objects systematically varied in size and interactive properties, biological stimuli, and food. The results showed that pre-weanlings initiated specific stimulus exploration faster, and were more interactive, with most of these stimuli than adults; the magnitude of these pre-weanling-adult quantitative differences ranged from fairly small to very large depending upon the stimulus. In contrast, pre-weanlings were adult-like in their interaction with food and prey. Interestingly, pre-weanling responses to live pups, was qualitatively different from that of adults; the preweanling behavioral repertoire was characterized by pup-seeking while the adult response was characterized by pup-avoidance. The specific stimulus interactions of pre-weanlings were less impacted than those of adults by the time of day of testing and placement of a stimulus in an anxiety-provoking location. The impact of novelty was stimulus dependent. The differences in interactions of pre-weanlings versus adults with specific environmental stimuli suggests that CNS systems underlying these behavior patterns are at different stages of immaturity at PND 18 such, and that there may be an array of developmental trajectories for responding to different categories of environmental stimuli. The results of this study provide a basis for the use of the pre-weanling rat as a preclinical model for understanding and medicating human disorders during development that are characterized by dysfunctional interactions with specific stimuli. Smith KS, Morrell JI. Behavioral differences between late preweanling and adult female Sprague-Dawley rat exploration of animate and inanimate stimuli and food.

Behavioral Brain Research. 2010. Sep 17 [online].

Differences Between Adolescent Boys and Girls in the Correlation of Emotional Control and Amygdala Volumes

Sex differences have been identified for the vulnerability to acquire drug abuse behaviors and progress to addiction. Problems in emotional regulation have been recognized as an early risk factor for a number of adverse developmental trajectories, including drug abuse and other co-morbid disorders. Development of these regulatory processes during late childhood and adolescence parallels the developmental period of greatest drug abuse vulnerability. Drs. Tara Chapin, Rajita Sinha and colleagues at Yale are studying sex differences in the brain regulation of emotion control during childhood and adolescence. The development of emotion regulation, including the ability to control emotions to meet situational demands, is an important developmental task. It is particularly important in adolescence, when youth must regulate emotions to meet environmental demands. The improvements in affective regulation and identification of emotional cues occur during the transition of adolescence are believed to involve the maturation of orbitofrontal and dorsolateral areas of the frontal lobe. This maturation of frontal areas allows for the regulation of subcortical nuclei such as the amygdala, which in particular, through its connections with the autonomic nervous system, leads to physiological arousal during emotional situations via activation of b-adrenergic receptors. This study involved the examination of male and female adolescents (8-18 years of age) scanned with structural brain MRI. Correlations were examined between volume of the right or the left amygdala and parent-reported emotional control. The results revealed sex differences in the correlation between emotional control and the corrected volume of the left amygdala (amygdala volume adjusted for total cranial volume). More specifically, in girls, smaller left amygdala volumes were associated with better emotional control. On the other hand, in boys, larger left amygdala volumes were associated with better emotional control. These findings suggest that healthy girls and boys show a difference in the correlation between parental reports of emotional control and volume in this important subcortical limbic structure, during adolescent development. Blanton RE, Chaplin TM, Sinha R. Sex differences in the correlation of emotional control and amygdala volumes in adolescents. *NeuroReport*. 2010; 21(14): 953-957.

Menstrual Cycle and Smoking Cue Reactivity in Women Smokers

Emerging research suggests potential effects of the menstrual cycle on various aspects of smoking behavior in women. Some studies, for example, have suggested that nicotine withdrawal and craving may be more severe during the luteal phase. The present study conducted by Dr. Kevin Gray and colleagues at the Medical University of South Carolina explored the influence of menstrual cycle phase on smoking cue reactivity and stressful imagery cues in a sample of 37 non-treatment-seeking nicotine-dependent women smokers recruited from the community. Via a within-subjects design, volunteers participated in a series of four cue reactivity sessions, each during a distinct biologically verified phase of the menstrual cycle: early follicular [EF], mid-follicular [MF], mid-luteal [ML], and late luteal [LL]. After smoking 45-60 min prior to the procedure, participants were exposed to four cues (90 s each, counterbalanced and separated by 10-min nature slide show). Active cues consisted of (a) in vivo manipulation of smoking paraphernalia and (b) imagery-based script of personalized stress-inducing event. Inactive/control cues consisted of (a) in vivo manipulation of pencil and eraser and (b) imagery-based script of relaxing event. Prior work by these researchers has shown these active cues to reliably induce craving relative to control cues. Subjective (Questionnaire of Smoking Urges-Brief; QSU-B) and physiological (heart rate and skin conductance) measures of craving and reactivity were

collected and compared across phases. The researchers found that subjective reactive craving (QSU-B) to smoking in vivo cues varied significantly across the menstrual cycle ($p = .02$) and was higher in both EF and MF phases versus ML and LL phases, but this finding was not sustained when controlling for reactivity to neutral cues. In contrast, heart rate reactivity to stressful imagery cues ($p = .01$) and skin conductance reactivity to smoking in vivo cues ($p = .05$) varied significantly across the menstrual cycle upon controlling for reactivity to neutral cues, with highest reactivity occurring during the MF phase. These data show that menstrual cycle phase can have an effect on reactivity to smoking-related and stressful cues among nicotine-dependent women smokers. These findings contribute to an expanding literature suggesting menstrual cycle effects on smoking behaviors in women. They raise the possibility that women who smoke in response to stress and/or cigarette cues may have greater difficulty trying to quit in the follicular phase than in the luteal phase. Future studies should investigate this possibility. Gray KM, DeSantis SM, Carpenter MJ, Saladin ME, LaRowe SD, Upadhyaya HP. Menstrual cycle and cue reactivity in women smokers. *Nicotine Tob Res.* 2010 Feb; 12(2): 174-178.

Characterization of the Dopamine Receptor System in Adult Rhesus Monkeys Exposed to Cocaine Throughout Gestation

Cocaine use during pregnancy is associated with alterations in the dopamine (DA) system in the fetal brain. However, little is known about the effects of prenatal cocaine exposure on the postnatal dopaminergic system. Dr. Michael Nader and his colleagues at Wake Forest School of Medicine sought to examine DA receptor function in adult monkeys that were prenatally exposed to cocaine. Male and female rhesus monkeys (approximately 13 years old) that had been prenatally exposed to cocaine ($n = 10$) and controls ($n = 10$) were tested in three studies. First, DA D2-like receptor availability was assessed using positron emission tomography (PET) and the D2-like receptor radiotracer [(18)F]fluorocleboipride (FCP). Next, D3 receptor function was assessed by measuring quinpirole-induced yawning (0.03-0.3 mg/kg). Finally, D1-like receptor function was examined by measuring eye blinking elicited by the high-efficacy D1-like receptor agonist SKF81297 (0.3-3.0 mg/kg). This unconditioned behavior is regarded as a sensitive measure of D1 signaling. Analysis of D2-like receptor availability in the caudate nucleus, putamen or amygdale revealed no differences between groups or sexes. Prior work has shown significantly higher levels of D2-like receptor densities in the fetal monkey striatum following gestational cocaine exposure. Data from the present study suggest that any changes in D2-like receptor availability that may have occurred in utero or in the developing brain had recovered in adulthood. Analysis of D3 receptor function indicated that quinpirole elicited significantly more yawns in prenatally cocaine-exposed monkeys compared with control monkeys. Additionally, a significant correlation between gestational dose of cocaine and peak effects of quinpirole was observed. Male monkeys, irrespective of their prenatal condition, yawned more following 0.03 mg/kg quinpirole compared with female monkeys. The greater ability of quinpirole to elicit yawning in the prenatally cocaine-exposed monkeys is similar to research demonstrating that rat pups exposed to cocaine throughout gestation exhibited a supersensitivity to the stimulating effects of quinpirole, with respect to behaviors such as forward locomotion, rearing, and directed oral movements, compared with control pups. Taken together, the present results provide evidence for long-term neuropharmacological consequences of prenatal cocaine exposure on D3 receptor function under conditions in which no difference in D2-like receptors was observed using PET imaging. Analysis of D1-like receptor function indicated that in all monkeys, administration of SKF81297 elicited dose-dependent increases in eye blinks that did not differ between prenatally cocaine-exposed monkeys and control monkeys. For both groups and across all SKF81297 doses, males blinked more than females. Prenatal cocaine has been reported to result in significant increases in D1-like receptor densities in fetal

monkey striatum, and in rodent and rabbit models several studies suggest that prenatal cocaine exposure uncouples the D1 receptor from its G-protein, resulting in an attenuation of D1 receptor signaling. Data from the present study suggest that any functional differences in D1-like receptor sensitivity observed in prenatally cocaine-exposed animals shortly after birth are no longer apparent in these animals as adults. It remains possible that other functional measures of D1-like receptor activity (e.g., drug discrimination or drug self-administration) may yield differential sensitivity due to prenatal cocaine exposure. In addition to these findings on prenatal cocaine exposure, the results are the first to note sex differences in sensitivity to D1-like agonist effects elicited by SKF 81297. DA D3 receptor function (quinpirole-elicited yawning) was also differentially affected by sex. Taken together, these findings indicate that prenatal cocaine exposure can have long-term effects on DA D3 receptor function in adults, and that males and females are equally sensitive to these perturbations. The present findings add to a growing body of evidence for sex differences in the behavioral effects of drugs. Hamilton LR, Czoty PW, Gage HD, Nader MA. Characterization of the dopamine receptor system in adult rhesus monkeys exposed to cocaine throughout gestation. *Psychopharmacology*. 2010 Jul; 210(4): 481-488.

Cocaine-induced Chromatin Remodeling Increases BDNF Transcription in the Rat mPFC and Decreases the Reinforcing Efficacy of Cocaine

A growing body of evidence indicates that cocaine exposure can alter the expression of neurotrophic factors in the brain. This study investigated the molecular mechanisms underlying changes in brain-derived neurotrophic factor (BDNF) in the rat medial prefrontal cortex (mPFC). Rats that self-administered cocaine for 14 days, followed by 7 days of forced abstinence, had elevated levels of BDNF protein in the mPFC compared to yoked saline control animals. The investigators next demonstrated the functional relevance of this finding by testing the effect of short hairpin RNA-induced suppression of BDNF expression in the mPFC on cocaine self-administration maintained under a progressive ratio schedule. They found that decreased BDNF expression in the mPFC increased the cocaine self-administration breakpoint. Next, they assessed the effect of cocaine self-administration on specific BDNF exons and found that cocaine selectively increased BDNF exon IV-containing transcripts in the mPFC. In addition, the cocaine exposure induced increases in acetylated histone H3 (AcH3) and phospho-cAMP response element binding protein (pCREB) association with BDNF promoter IV, while it decreased methyl-CpG-binding protein 2 (MeCP2) association with BDNF promoter IV. Together, these results indicate that cocaine-induced increases in BDNF promoter IV transcript in the mPFC are driven by increased binding of AcH3 and pCREB and decreased MeCP2 binding at this BDNF promoter. These results indicate that cocaine self-administration remodels chromatin in the mPFC, resulting in increased expression of BDNF. Previous studies in other brain areas, e.g., the nucleus accumbens, suggest that increases in BDNF can augment cocaine reinforcement, but the current study suggests that the BDNF increase in mPFC is, effectively, a compensatory neuroadaptation that reduces the reinforcing efficacy of cocaine. Sadri-Vakili G, Kumaresan V, Schmidt HD, Famous KR, Chawla P, Vassoler FM, Overland RP, Xia E, Bass CE, Terwilliger EF, Pierce RC, Cha JH. Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine. *J Neurosci*. 2010 Sep 1; 30(35): 11735-11744.

Cocaine Produces Long-lasting Increases in Impulsive Choice

Human cocaine users are more impulsive than non-users. This difference can be seen on a delay discounting task, where users show a preference for

immediate, smaller rewards over larger, delayed rewards. Animal studies can be used to investigate whether this difference is a trait that predisposes an individual to become a long-term cocaine user, or whether exposure to cocaine itself increases impulsive choice, or both. In the current study, Dr. Barry Setlow and colleagues examined the effects of prior cocaine self-administration on delay discounting in rats. They trained rats to self-administer cocaine for 14 days, and used a control group that received yoked intravenous saline infusions. After 3 weeks of withdrawal, the rats began training on the delay discounting task. When tested approximately 3 months after their last exposure to cocaine, rats that had self-administered the drug showed a preference for small immediate rewards compared to the control animals. These results confirm the investigators' prior results with experimenter-administered cocaine, but they are important because self-administration more closely models human drug use, and other studies have shown that self-administered cocaine can have different effects than experimenter-administered cocaine on a number of behavioral and neurobiological outcomes. The researchers also tested the rats on another choice task, probabilistic discounting. In this task, rats have a choice between a smaller, certain reward (1 food pellet) versus a larger reward (3 pellets) with a decreasing probability (100%, 75%, 50%, 25% and 0%). In this test, both groups of rats behaved similarly: their choice of the larger reward was high for the first 3 conditions, decreased when the probability dropped to 25%, and decreased markedly when the probability was 0. This dissociation between delay versus probabilistic discounting has also been found in human cocaine users, and suggests that cocaine specifically effects temporal decision making rather than general factors such as incentive motivation, sensitivity to reward magnitude, or the ability to discriminate between different reward conditions. Mendez IA, Simon NW, Hart N, Mitchell MR, Nation JR, Wellman PJ, Setlow B. Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. *Behav Neurosci.* 2010 Aug; 124(4): 470-477.

Effects of Methamphetamine on Sexual Behavior in Rats

Methamphetamine (meth) abuse is often linked with risky sexual behavior and increased risk for HIV infection. However, the nature of this association is unclear from human studies. This study by Dr. Lique Coolen and colleagues sought to examine the effects of meth on aspects of male sexual behavior in a rat model. The first experiment tested the effects of different doses (1, 2, and 4 mg/kg) of meth on sexual performance in sexually experienced and naive male rats. Meth inhibited sexual performance at the two highest doses in naive animals and at the highest dose only in experienced animals. A second experiment was designed to determine whether meth exposure would produce maladaptive sexual behavior. To test this, the investigators used a conditioned aversion paradigm, similar to that used for conditioned taste aversion. That is, immediately after a sexual experience with a receptive female, male rats were injected with either LiCl to induce illness (paired group), or with saline as a control. The animals treated with saline were injected with LiCl a day later (unpaired group). Animals in the paired group that had been pretreated with a single dose of 1 mg/kg meth (which did not impair performance) before the conditioning sessions started, required more sessions to develop conditioned aversion to sexual behavior, compared to saline pretreated animals. No animals in the unpaired group developed an aversion. Furthermore, after the conditioned aversion was established, sexual seeking was partially restored by a single dose of meth in the animals that had received meth pretreatment. These results suggest that meth can impair sexual motivation and performance. Also, they suggest that low doses of meth which are sub-threshold for disrupting sexual function produce maladaptive, or "risky," sexual behavior in an animal model. Frohmader KS, Bateman KL, Lehman MN, Coolen LM. Effects of methamphetamine on sexual performance and compulsive sex behavior in male rats. *Psychopharmacology (Berl).* 2010 Sep; 212(1): 93-104.

Preclinical Studies Show Promising Results for Modafinil as a Therapeutic Agent for Relapse

Modafinil (Provigil) is prescribed for treatment of narcolepsy and has cognitive enhancing effects. Several recent small clinical studies suggest that modafinil may be useful for treatment of chronic psychostimulant addiction and for preventing relapse. These studies were premised on the hypothesis that modafinil might improve cognition, impulse control, and mood, which should improve resistance to renewed drug taking. The exact mechanisms of modafinil's effects on the brain are unknown: its beneficial results for narcolepsy have been attributed to orexin receptor activation, but it also interacts with many catecholamine and amino acid transmitter systems. Modafinil has not been tested in animal models of drug addiction, which is an essential step in developing pharmacotherapy for addiction, because studies in animal models can be used to discover mechanisms, range of effects, and abuse liability of potential medications. Now, two laboratories at the Medical University of South Carolina have begun such studies. Dr. Ron See and his colleagues investigated modafinil effects in reinstatement of methamphetamine (meth) seeking in a rat relapse model. Rats were trained to self administer meth and then they underwent a period of abstinence or extinction training. Modafinil was administered during reinstatement tests, where reinstatement was induced by drug-associated cues, drug priming, or the drug context. They found that modafinil attenuated reinstatement under all three conditions, and importantly, modafinil alone did not reinstate meth seeking. The second study by Dr. Gary Aston-Jones and colleagues investigated modafinil's effects on the reinstatement of extinguished opiate-seeking using conditioned place preference (CPP). This study is of interest because modafinil has never been tested in clinical studies of opiate users, and in addition, the study examined the involvement of group II metabotropic glutamate receptors (mGlu2/3Rs), which have been suggested as a new therapeutic target. Modafinil administered 30 minutes before a reinstatement test was effective in blocking reinstatement of extinguished morphine CPP induced by a priming injection. Furthermore, the anti-reinstatement effect of modafinil was completely prevented by pretreatment with the selective mGlu2/3 antagonist, LY341495. Importantly, similar to findings from Dr. See's study, modafinil did not appear to have reinforcing effects: when given alone, it did not induce place conditioning nor reinstate drug-seeking either 1 or 14 days after extinction of the morphine CPP. Together, these studies support clinical findings in humans to suggest that modafinil may be effective in preventing relapse in abstinent meth users, and further suggest that modafinil should be tested in opiate users as well. Further, the second study supports a role for mGlu2/3 receptors in reinstatement of opiate-seeking. Reichel CM, See RE. Modafinil effects on reinstatement of methamphetamine seeking in a rat model of relapse. *Psychopharmacology (Berl)*. 2010 Jun; 210(3): 337-346. Tahsili-Fahadan P, Carr GV, Harris GC, Aston-Jones G. Modafinil blocks reinstatement of extinguished opiate-seeking in rats: mediation by a glutamate mechanism. *Neuropsychopharmacology*. 2010 Oct; 35(11): 2203-2210.

Cannabinoid-2 Receptor Activation Produces Analgesia Independent of Opioid Effects

Activation of CB2 receptors may provide a therapeutic target for the treatment of pain that circumvents unwanted central side effects associated with activation of CB1 receptors. One of the primary CB2 agonists used in research is (R,S)-AM1241. However, (R,S)-AM1241 may produce antinociception mediated indirectly by opioid receptors, thus limiting its potential clinical use due to problems associated with opiates such as tolerance, dependence and the development of hyperalgesia. In the current ARRA-funded study, NIDA-grantee Dr. Andrea Hohmann (University of Georgia) and collaborators

examined (R,S)-AM1241 and its enantiomers, (R)-AM1241 and (S)-AM1241 in behavioral tests of thermal antinociception and mechanical allodynia in rats. (R,S)-AM1241, (R)-AM1241, and (S)-AM1241 (0.033-10 mg/kg i.p.) produced antinociception to thermal, but not mechanical, stimulation of the hindpaw in naive rats. Local and systemic naloxone blocked morphine-induced antinociception but did not block antinociceptive effects of (R,S)-AM1241, (R)-AM1241, or (S)-AM1241. Thus, the antinociceptive effects of the CB2-selective cannabinoid (R,S)-AM1241 and its enantiomers, (R)-AM1241 and (S)-AM1241, are not dependent upon opioid receptors, which bolsters their potential for clinical application. Rahn, EJ, Zvonok, AM, Makriyannis, A. and Hohmann, AG, Antinociceptive effects of racemic AM1241 and its chirally synthesized enantiomers: Lack of dependence upon opioid receptor activation. The American Association of Pharmaceutical Scientists Journal. 2010: 12: 147-157.

Midbrain Neurons That Fire as "Off" Cells During Analgesia May Also Protect Sleep

NIDA grantee Dr. Peggy Mason (University of Chicago) and her colleagues recently examined the role of classic pain modulation cells in the rostral ventral medulla (RVM) in waking and arousal. Dr. Mason examined if waking evoked by an innocuous air-puff is affected by intra-RVM administration of neurotensin and bicuculline, pharmacological manipulations that affect "on" and "off" cell activity. Air-puff evoked arousal was unaffected by 0.05 ng neurotensin. However, doses of 502 ng neurotensin, and 5 and 50 ng bicuculline that produce analgesia by activating "off" midbrain neurons, resulted in less air puff arousal, suggesting a role for these neurons in protecting sleep from incoming non-noxious stimulation. Foo, H, Crabtree, K, Mason, P. The modulatory effects of rostral ventromedial medulla on air-puff evoked microarousals in rats, Behavioral Brain Research. 2010: (215): 156-159.

Evidence for Multiple Pain Facilitation Pathways

Inhibition of pain facilitatory neurons in the rostral ventromedial medulla (RVM) is one mechanism by which mu opioid receptor agonists produce analgesia. The analgesic effects of a mu opioid receptor agonist, DAMGO, are enhanced after inflammation of the rat paw. NIDA-grantee Dr. Donna Hammond (University of Iowa) examined whether paw inflammation enhanced the ability of DAMGO to induce outward currents in spinally projecting RVM neurons and if these currents are modified by paw inflammation. Whole-cell patch clamp recordings were made from three types of serotonergic as well as non-serotonergic spinally projecting RVM neurons obtained from rats four days following inflammation, or in control rats. Persistent, but not acute inflammatory pain increased the percentage of Type 2 non-serotonergic neurons that responded to DAMGO from 17% to 57%, and the percentage of Type 3 serotonergic neurons that responded to DAMGO from 5% to 55%. These results provide intriguing evidence for two different populations of pain facilitatory neurons in the RVM involved with chronic pain. Zhang L, Hammond DL. Cellular basis for opioid potentiation in the rostral ventromedial medulla of rats with persistent inflammatory nociception. Pain. 2010: (149): 107-116.

Adolescent Drug Sensitivity is Enhanced by Prior Exposure to Drug-Treated Conspecifics

Adolescence is a period of vulnerability to drug abuse and early drug exposure is associated with later substance abuse problems. It is also a period of intense social interactions and peer influences are important for the initiation of drug abuse. Animal studies have revealed differences in acute drug response, and the development of tolerance or sensitization, in adolescent versus adult animals. NIDA supported researchers at UCLA and Texas A&M University have

assessed the influence of group housing with drug-treated conspecifics, on subsequent sensitivity to morphine, in adolescent versus adult mice. Drug-treated mice were injected twice daily for six days with escalating doses of s.c. morphine, while control animals received saline. Controls were divided into two different groups - half were housed with morphine-injected mice, and half were housed with saline only treated animals, in groups of four. Thus, groups of four mice each were made up of 2 saline treated + 2 morphine treated, or 4 saline treated animals. All morphine treated mice developed sensitization to the locomotor stimulating effects of this drug, whereas saline injected mice showed no change in locomotor activity. Interestingly, saline-treated adolescent mice that were housed with morphine treated adolescents, (housed 2 morphine + 2 saline mice), when tested with acute morphine after the chronic injection regimen, showed an exaggerated behavioral response to the opiate. However, adult animals housed under the same conditions did not have an exaggerated locomotor response when challenged with acute morphine. This finding indicates that the social experience with drug-treated animals, or social interaction during the morphine intoxication period, sensitized saline-treated animals to morphine's behavioral effects. The investigators suggest that housing with morphine-intoxicated, or morphine-withdrawn mice, might expose saline treated adolescent mice to heightened levels of stress. Alternatively, morphine treatment may provoke aggressive interactions during these housing conditions, or olfactory cues (pheromones) from morphine treated mice may affect the saline treated housemates. These influences are without effect in comparably treated adults, and highlight a particular sensitivity to social factors in the environment, on sensitivity to drugs of abuse during the adolescent period of development. This behavioral paradigm can subsequently be used to examine the generality of this phenomenon with other drugs of abuse, examine sex differences, and probe the neurobiological mechanisms of the effect. Hodgson SR, Hofford RS, Roberts KW, Wellman PJ, Eitan S. Socially induced morphine pseudosensitization in adolescent mice. *Behav Pharmacol.* 2010. 21(2): 112-120.

The Progesterone Metabolite, Allopregnanolone, Blocks Escalation of Cocaine Intake in Rats

Recent animal research and human laboratory based studies suggest that the progesterone metabolite, allopregnanolone (ALLO), may reduce drug taking of cocaine over several different phases of the abuse cycle. For example, progesterone administration during the follicular phase reduces the positive subjective effects of cocaine, and ALLO decreases cocaine-seeking in an animal model of stress-induced relapse. Recently Dr. Marilyn Carroll and colleagues sought to determine if ALLO would have similar attenuating effects on compulsive drug taking in female rats, seen using a long-access paradigm. In this procedure, rats are first trained to self-administer i.v. cocaine and then control animals continue to self-administer drug for 2h per day. Experimental subjects are switched to 6h/day access and typically develop increased cocaine intake over continued daily access. Dr. Carroll hypothesized that ALLO would confer protection against the development of binge-like patterns of cocaine intake. ALLO treated animals were injected each day before self-administration and controls received vehicle instead. Different groups of animals were tested for ALLO effects under a progressive ratio (PR) operant schedule, which measures the maximum number of responses an animal will make to receive drug, while others were tested with the 6h/day escalation procedure for a sucrose reinforcer instead of drug. Results confirm that daily ALLO treatment before the drug self-administration sessions blocked the development of escalated intake in the long-access (6h/day) group but was without effects on rats self-administering for 1h/day (short access). By contrast, ALLO pretreatment did not alter cocaine intake in the progressive ratio test, using a short-access procedure. Thus, ALLO did not affect an animal's "willingness" to respond for cocaine. ALLO was also without effect on the number of responses

made for sucrose when it was provided under a long access procedure or for sucrose during 2h/day sessions with yohimbine-induced stress used to elevate responding for this natural reinforcer. The researchers suggest that ALLO may block the development of compulsive cocaine taking via its action as an allostatic modulator of GABA-A receptors - a pharmacological action that antagonizes effects of corticotrophin releasing factor (CRF). Thus, while ALLO is without effects on the subjective, reinforcing effects of cocaine seen with PR testing, its effects on binge-like patterns of drug intake may be via its effects on dampening stress. Few studies have extended these animal results to human testing, although reports that ALLO suppresses alcohol withdrawal symptoms indicates that it may be a clinically useful approach in the pharmacotherapy for cocaine addiction. Anker JJ, Zlebnik NE, Carroll ME. Differential effects of allopregnanolone on the escalation of cocaine self-administration and sucrose intake in female rats. *Psychopharmacology (Berl)*. 2010 Oct; 212(3): 419-429.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Behavioral and Brain Development Research

Lack of Concordance between Teen Report and Biological Measures of Drug Use

Prevalence estimates of illicit drug use by teens are typically generated from confidential or anonymous self-report. While data comparing teen self-report with biological measures are limited, adult studies identify varying degrees of under-reporting. Dr. Virginia Delaney-Black and her colleagues at Wayne State University compared hair analyses for cocaine, opiates and marijuana to confidential teen self- and parent-reported teen drug use in a longitudinal cohort of >400 high-risk urban teens and parents, including teens exposed to cocaine in utero. Both teens and parents substantially underreported recent teen cocaine and opiate use. However, compared with parents, teens were more likely to deny biomarker-verified cocaine use. Teen specimens (hair) were 52 times more likely to identify cocaine use compared with self-report. Parent hair analyses for cocaine and opiate use were 6.5 times and 5.5 times, respectively, more likely to indicate drug use than were parental self-report. The lack of concordance between self-report and bioassay occurred despite participant's knowledge that a "certificate of confidentiality" protected both teen and adult participants, and that the biological specimens would be tested for drugs. These findings confirm prior reports of adult under-reporting of their own drug use while extending our understanding of teens' self-admitted drug use. The lack of concordance between teen self- or parent-reported teen drug use and biomarkers confirm our concerns that both teen- and parent-reported teen drug use is limited, at least for youth in high-risk urban settings. Methods of ascertainment other than self- or parent-report must be considered when health care providers, researchers and public health agencies attempt to estimate teen drug-use prevalence. Delaney-Black V, Chiodo LM, Hannigan JH, Greenwald MK, Janisse J, Patterson G, Huestis MA, Ager J, Sokol RJ. Just say "I don't": Lack of concordance between teen report and biological measures of drug use. *Pediatrics*. 2010 Nov; 126(5): 887-893.

Risky Decisions and Their Consequences: Neural Processing by Boys with Antisocial Substance Disorder

Adolescents with conduct and substance problems ("Antisocial Substance Disorder" [ASD]) repeatedly engage in risky antisocial and drug-using behaviors. The purpose of this study was to examine whether brain activation would differ between abstinent ASD boys and comparison boys during processing of risky decisions and resulting rewards and punishments. Dr. Crowley and his colleagues at the University of Colorado Denver compared 20 abstinent adolescent male patients in treatment for ASD with 20 community controls, examining rapid event-related blood-oxygen-level-dependent (BOLD)

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responses during functional magnetic resonance imaging. In 90 decision trials, participants chose to make either a cautious response that earned one cent, or a risky response that would either gain 5 cents or lose 10 cents; odds of losing increased as the game progressed. Those times when subjects experienced wins, or separately losses, from their risky choices were also examined. Decision trials against very similar comparison trials requiring no decisions were examined, using whole-brain BOLD-response analyses of group differences, corrected for multiple comparisons. During decision-making ASD boys showed hypoactivation in numerous brain regions robustly activated by controls, including orbitofrontal and dorsolateral prefrontal cortices, anterior cingulate, basal ganglia, insula, amygdala, hippocampus, and cerebellum. While experiencing wins, ASD boys had significantly less activity than controls in anterior cingulate, temporal regions, and cerebellum, with more activity nowhere. During losses ASD boys had significantly more activity than controls in orbitofrontal cortex, dorsolateral prefrontal cortex, brain stem, and cerebellum, with less activity nowhere. Adolescent boys with ASD had extensive neural hypoactivity during risky decision-making, coupled with decreased activity during reward and increased activity during loss. These neural patterns may underlie the dangerous, excessive, sustained risk-taking of such boys. The findings suggest that the dysphoria, reward insensitivity, and suppressed neural activity observed among older addicted persons also characterize youths early in the development of substance use disorders. Crowley TJ, Dalwani MS, Mikulich-Gilbertson SK, Du YP, Lejuez CW, Raymond KM, Banich MT. Risky decisions and their consequences: Neural processing by boys with Antisocial Substance Disorder. *PLoS One*. 2010 Sep 22; 5(9): e12835.

Examining Manual and Visual Response Inhibition among ADHD Subtypes

This study compared inhibitory functioning among ADHD subtype groups on manual and visual versions of the stop task. Seventy-six children, identified as ADHD/I (ADHD/I = ADHD inattentive, n=17), ADHD/C (ADHD/C = ADHD combined, n=43), and comparison (n=20) completed both tasks. Results indicated that both ADHD groups were slower to inhibit responses than the comparison group on both tasks. Comparison children were faster to inhibit than activate responses on both tasks. Children in the ADHD groups also demonstrated this robust pattern on the manual task. However, on the visual task, the ADHD groups evidenced slowed inhibition comparable to the time required to activate responding. This implies that the visual task is more sensitive than the manual task to inhibitory deficits associated with ADHD. The ADHD/I and the ADHD/C groups did not differ on most measures, suggesting that neither stop task is effective in differentiating the subtypes. These findings extend work highlighting the role of disinhibition in ADHD, and contrast recent work suggesting divergence between ADHD subtypes. Adams ZW, Milich R, Fillmore MT. Examining manual and visual response inhibition among ADHD subtypes. *J Abnorm Child Psychol*. 2010 Oct; 38(7): 971-983.

The Influence of Recency of Use on fMRI Response during Spatial Working Memory in Adolescent Marijuana Users

Some neurocognitive recovery occurs within a month of abstinence from heavy marijuana use, yet functional magnetic resonance imaging (fMRI) has revealed altered activation among recent and abstinent adult users. An investigative team at Yale University compared fMRI response during a spatial working memory (SWM) task between adolescent marijuana users with brief and sustained durations of abstinence. Participants were 13 recent users (two to seven days abstinent), 13 abstinent users (27 to 60 days abstinent), and 18 nonusing controls, all ages 15 to 18. Groups were similar on demographics,

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had no psychiatric or medical disorders, and user groups were similar on substance histories. Teens performed a two-back SWM task during fMRI. Recent users showed greater fMRI response in medial and left superior prefrontal cortices, as well as bilateral insula. Abstinent users had increased response in the right precentral gyrus (clusters ≥ 1328 microl, $p < .05$). Results suggest that adolescents who recently used marijuana show increased brain activity in regions associated with working memory updating and inhibition. This study preliminarily suggests that (1) recent marijuana use may disrupt neural connections associated with SWM and result in compensatory brain response, and (2) sustained abstinence from marijuana may be associated with improvements in SWM response among adolescents. Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeney T, Brown SA, Tapert SF. The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. *J Psychoactive Drugs*. 2010 Sep; 42(3): 401-412.

Puberty Influences Medial Temporal Lobe and Cortical Gray Matter Maturation Differently in Boys Than Girls Matched for Sexual Maturity

Sex differences in age- and puberty-related maturation of human brain structure have been observed in typically developing age-matched boys and girls. Because girls mature 1-2 years earlier than boys, the present study aimed at assessing sex differences in brain structure by studying 80 adolescent boys and girls matched on sexual maturity, rather than age. Pubertal influences on medial temporal lobe (MTL), thalamic, caudate, and cortical gray matter volumes utilizing structural magnetic resonance imaging and 2 measures of pubertal status: Physical sexual maturity and circulating testosterone were examined. As predicted, significant interactions between sex and the effect of puberty were observed in regions with high sex steroid hormone receptor densities; sex differences in the right hippocampus, bilateral amygdala, and cortical gray matter were greater in more sexually mature adolescents. Within sex, larger volumes in MTL structures in more sexually mature boys were found, whereas smaller volumes were observed in more sexually mature girls. These results demonstrate puberty-related maturation of the hippocampus, amygdala, and cortical gray matter that is not confounded by age, and is different for girls and boys, which may contribute to differences in social and cognitive development during adolescence, and lasting sexual dimorphisms in the adult brain. Bramen JE, Hranilovich JA, Dahl RE, Forbes EE, Chen J, Toga AW, Dinov ID, Worthman CM, Sowell ER. Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cereb Cortex*. 2010 Aug 16. [Epub ahead of print].

Learning and Memory Performances in Adolescent Users of Alcohol and Marijuana: Interactive Effects

Lifetime alcohol hangover and withdrawal symptoms in youth have been shown to predict poorer recall of verbal and nonverbal information, as well as reduced visuospatial skills. Some evidence has suggested that negative effects of alcohol on the brain may be buffered in part by potential neuroprotective properties of cannabinoids. This study examined whether a history of more alcohol hangover symptoms would predict worse performances on measures of verbal and visual memory, and that this relationship would be moderated by marijuana involvement. Participants were 130 adolescents (65 with histories of heavy marijuana use, and 65 non-marijuana-using controls), ranging in age from 15.7 to 19.1 years. Neuropsychological tests for visual and verbal memory and interviews assessing lifetime and recent substance use, hangover/withdrawal symptoms, and abuse and dependence criteria were administered. Regression models revealed that greater alcohol hangover

symptoms predicted worse verbal learning ($p < .05$) and memory ($p < .05$) (California Verbal Learning Test, Second Edition) scores for non-marijuana users, but alcohol hangover symptoms were not linked to performance among marijuana users. Alcohol hangover symptoms did not predict visual memory in either group. Results confirm previous studies linking adolescent heavy drinking to reduced verbal learning and memory performance. However, this relationship is not seen in adolescents with similar levels of alcohol involvement who also are heavy users of marijuana. Mahmood OM, Jacobus J, Bava S, Scarlett A, Tapert SF. Learning and memory performances in adolescent users of alcohol and marijuana: Interactive effects. *J Stud Alcohol Drugs*. 2010 Nov; 71(6): 885-894.

Associations of Marijuana Use and Sex-related Marijuana Expectancies with HIV/STD Risk Behavior in High-risk Adolescents

Multiple studies suggest an association of marijuana use with increased rates of sexual risk behavior and sexually transmitted diseases (STDs). Most studies have focused on global associations of marijuana use with sexual risk outcomes and few have examined relevant cognitive variables. Adolescents in the juvenile justice system are at elevated risk for HIV/STDs and preliminary evidence suggests that marijuana is a potentially important cofactor for sexual risk behavior in this population. This study by Dr. Angela Bryan and colleagues evaluated global, situational and event-level associations of marijuana use and sex-related marijuana expectancies with sexual risk outcomes in a large, racially diverse sample of adjudicated youth ($n = 656$, 66% male, mean age = 16.7 years). Cross-sectional and prospective analyses identified associations of marijuana use and dependence symptoms with sexual risk outcomes, including lower frequency of condom use and higher STD incidence. Stronger sex-related marijuana expectancies predicted greater intentions for and frequency of marijuana use in sexual situations. In event-level analyses that controlled for alcohol, marijuana use predicted a significantly decreased likelihood of condom use; this association was moderated by sex-related marijuana expectancies. Mediation analyses suggested that behavioral intentions partly accounted for the prospective association of expectancies with marijuana use before sex. These results provide further evidence that marijuana use is a potentially important cofactor for HIV/STD transmission in high-risk adolescents and suggest that cognitive factors could be important for characterizing this association. Hendershot CS, Magnan RE, Bryan AD. Associations of marijuana use and sex-related marijuana expectancies with HIV/STD risk behavior in high-risk adolescents. *Psychol Addict Behav*. 2010 Sep; 24(3): 404-414.

Changes in Sensation Seeking and Risk-taking Propensity Predict Increases in Alcohol Use among Early Adolescents

Conceptual models implicating disinhibitory traits often are applied to understanding emergent alcohol use, but little is known of how inter-individual changes in these constructs relate to increases in alcohol use in early adolescence. The current study by Dr. Carl Lejuez and his colleagues at the University of Maryland utilized behavioral and self-report instruments to capture the disinhibitory-based constructs of sensation seeking and risk-taking propensity to examine if increases in these constructs over time related to increases in early adolescent alcohol use. Participants included a community sample of 257 early adolescents (aged 9 to 12) who completed a self-report measure of sensation seeking, a behavioral task assessing risk-taking propensity, and a self-report of past year alcohol use, at 3 annual assessment waves. Both sensation seeking and risk-taking propensity demonstrated significant increases over time. Greater sensation seeking and greater risk-taking propensity demonstrated concurrent relationships with past year alcohol use at each assessment wave. Prospective analyses indicated that after

accounting for initial levels of alcohol use, sensation seeking, and risk-taking propensity at the first assessment wave, larger increases in both constructs predicted greater odds of alcohol use at subsequent assessment waves. Results indicate the role of individual changes in disinhibitory traits in initial alcohol use in early adolescents. Specifically, findings suggest it is not simply initial levels of sensation seeking and risk-taking propensity that contribute to subsequent alcohol use but in particular increases in each of these constructs that predict greater odds of use. Future work should continue to assess the development of sensation seeking and risk-taking propensity in early adolescence and target these constructs in interventions as a potential means to reduce adolescent alcohol use. MacPherson L, Magidson JF, Reynolds EK, Kahler CW, Lejuez CW. Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. *Alcohol Clin Exp Res*. 2010 Aug; 34(8): 1400-1408.

Resting Brain and Risky Behavior

Research on the neural correlates of risk-related behaviors and personality traits has provided insight into mechanisms underlying both normal and pathological decision-making. Task-based neuroimaging studies implicate a distributed network of brain regions in risky decision-making. What remains to be understood are the interactions between these regions and their relation to individual differences in personality variables associated with real-world risk-taking. Dr. Xavier Castellanos and colleagues at NYU employed resting state functional magnetic resonance imaging (R-fMRI) and resting state functional connectivity (RSFC) methods to investigate differences in the brain's intrinsic functional architecture associated with beliefs about the consequences of risky behavior. An individual measure of expected benefit from engaging in risky behavior, indicating a risk-seeking or risk-averse personality, was obtained for each of 21 participants from whom were also collected a series of R-fMRI scans. The expected benefit scores were entered in statistical models assessing the RSFC of brain regions consistently implicated in both the evaluation of risk and reward, and cognitive control (i.e., orbitofrontal cortex, nucleus accumbens, lateral prefrontal cortex, dorsal anterior cingulate). The team specifically focused on significant brain-behavior relationships that were stable across R-fMRI scans collected one year apart. Two stable expected benefit-RSFC relationships were observed: Decreased expected benefit (increased risk-aversion) was associated with 1) stronger positive functional connectivity between right inferior frontal gyrus (IFG) and right insula, and 2) weaker negative functional connectivity between left nucleus accumbens and right parieto-occipital cortex. Task-based activation in the IFG and insula has been associated with risk-aversion, while activation in the nucleus accumbens and parietal cortex has been associated with both risk seeking and risk-averse tendencies. Results suggest that individual differences in attitudes toward risk-taking are reflected in the brain's functional architecture and may have implications for engaging in real-world risky behaviors. Cox, CL, Gotimer K, Roy AK, Castellanos FX, Milham MP, Kelly C. Your resting brain CAREs about your risky behavior. *PLoS One*. 2010 Aug 19; 5(8): e12296.

Identifying Prenatal Cannabis Exposure and Effects of Concurrent Tobacco Exposure on Neonatal Growth

Cannabis is the most frequently used illicit drug among pregnant women, but data describing the effects of prenatal cannabis exposure and concurrent nicotine and cannabis exposures on neonatal growth are inconsistent. Testing of meconium, the first neonatal feces, offers objective evidence of prenatal cannabis exposure, but the relative ability of meconium testing and maternal self-report to identify affected neonates remains unclear. In this study by Dr. Rina Eiden and her colleagues at SUNY Buffalo and collaborator Dr. Marilyn Huestis, NIDA IRP, 86 pregnant women provided detailed self-reports of daily

cannabis and tobacco consumption throughout pregnancy. Cannabinoids and tobacco biomarkers were identified in oral fluid samples collected each trimester and quantified in meconium at birth. Cannabis-using women were significantly more likely to also consume tobacco, and smoked similar numbers of cigarettes as non-cannabis-using tobacco smokers. As pregnancy progressed, fewer women smoked cannabis and those who continued to use cannabis reported smoking a smaller number of cannabis joints, but positive maternal oral fluid tests cast doubt on the veracity of some maternal self-reports. More neonates were identified as cannabis exposed by maternal self-report than meconium analysis, because many women quit cannabis use after the first or second trimester; meconium was more likely to be positive if cannabis use continued into the third trimester. Cannabis exposure was associated with decreased birth weight, reduced length, and smaller head circumference, even after data were controlled for tobacco coexposure. Prenatal cannabis exposure was associated with fetal growth reduction. Meconium testing primarily identifies prenatal cannabis exposure occurring in the third trimester of gestation. Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. *Clin Chem*. 2010 Sep; 56(9): 1442-1450.

Patterns of Methamphetamine Use During Pregnancy

The objectives of this study are to characterize methamphetamine (MA) usage patterns during pregnancy, examine whether patterns of MA use are associated with sociodemographic characteristics and prenatal care, and test the hypothesis that persistent or increasing MA use during pregnancy is associated with greater use of other illicit drugs. The sample consisted of 191 MA-using mothers who participated in a large-scale multi-site study of prenatal MA exposure conducted by Dr. Barry Lester and colleagues in Tusla, DesMoines, and Hawaii. Patterns of substance use were assessed by maternal self-report via the Substance Use Inventory (SUI), which included detailed information about MA use, including frequency, quantity, and maximum use during each trimester of pregnancy. The study demonstrated that on average, the prevalence of MA use decreased over the three trimesters of pregnancy (84.3% vs. 56.0% vs. 42.4%), and decreased frequency was observed among users from the first trimester to the third (3.1 vs. 2.4 vs. 1.5 days/week). Closer examination of the individual patterns revealed that 29.3% of women maintained consistently high frequency, 9.4% increased frequency, 25.7% had a stable low/moderate pattern, and 35.6% decreased their frequency of MA over the course of pregnancy. These four groups did not differ in sociodemographic characteristics; women who decreased their use of MA had significantly more prenatal visits compared to the consistently high-use group, but were the most likely to use alcohol during their pregnancy. In conclusion, approximately, one third of MA-using mothers could be classified as consistently high users with a profile of use with the greatest risk to themselves and potentially to their infants including high levels of MA use throughout pregnancy and fewer prenatal care visits. Overall, MA use declined across pregnancy; however, a substantial proportion of users had consistently high or increasing MA use, while those who decreased their MA frequency had a higher prevalence of polydrug use. Future research will investigate the association of these patterns with neonatal outcomes. Della Grotta S, LaGasse LL, Arria AM, Derauf C, Grant P, Smith LM, Shah R, Huestis M, Liu J, Lester BM. Patterns of methamphetamine use during pregnancy: Results from the Infant Development, Environment, and Lifestyle (IDEAL) Study. *Matern Child Health J*. 2010 Jul; 14(4): 519-527.

Drug Use During Pregnancy: Ecstasy Stops, Alcohol Consumption Reduced, Tobacco and Cannabis Use Continued

While recreational drug use in UK women is prevalent, to date there are little prospective data on patterns of drug use in recreational drug-using women immediately before and during pregnancy. A total of 121 participants from a wide range of backgrounds were recruited to take part in the longitudinal Development and Infancy Study (DAISY) study of prenatal drug use and outcomes conducted by Dr. Lynn Singer. Eighty-six of the women were interviewed prospectively while pregnant and/or soon after their infant was born. Participants reported on use immediately before and during pregnancy and on use over their lifetime. Levels of lifetime drug use of the women recruited were high, with women reporting having used at least four different illegal drugs over their lifetime. Most users of cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA) and other stimulants stopped using these by the second trimester and levels of use were low. However, in pregnancy, 64% of the sample continued to use alcohol, 46% tobacco and 48% cannabis. While the level of alcohol use reduced substantially, average tobacco and cannabis levels tended to be sustained at pre-pregnancy levels even into the third trimester (50 cigarettes and/or 11 joints per week). In sum, while the use of 'party drugs' and alcohol seems to reduce, levels of tobacco and cannabis use are likely to be sustained throughout pregnancy. The data provide polydrug profiles that can form the basis for the development of more realistic animal models. Moore DG, Turner JD, Parrott AC, Goodwin JE, Fulton SE, Min MO, Fox HC, Braddick FM, Axelsson EL, Lynch S, Ribeiro H, Frostick CJ, Singer LT. During pregnancy recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: Initial findings from the Development and Infancy Study. *J Psychopharmacol.* 2010 Sep; 24(9): 1403-1410.

Prenatal Methadone Exposure, Meconium Biomarker Concentrations and Neonatal Abstinence Syndrome

Methadone is standard pharmacotherapy for opioid-dependent pregnant women, yet the relationship between maternal methadone dose and neonatal abstinence syndrome (NAS) severity is still unclear. This research evaluated whether quantification of fetal methadone and drug exposure via meconium would reflect maternal dose and predict neonatal outcomes. Forty-nine opioid-dependent pregnant women receiving 30-110 mg methadone daily took part in this study. Maternal methadone dose, infant birth parameters and NAS assessments were extracted from medical records. Thrice-weekly urine specimens were screened for opioids and cocaine. Newborn meconium specimens were quantified for methadone, opioid, cocaine and tobacco biomarkers. There was no relationship between meconium methadone concentrations, presence of opioids, cocaine and/or tobacco in meconium, maternal methadone dose or NAS severity. Opioid and cocaine were also found in 36.7 and 38.8 of meconium specimens, respectively, and were associated with positive urine specimens in the third trimester. The presence of opioids other than methadone in meconium correlated with increased rates of preterm birth, longer infant hospital stays and decreased maternal time in drug treatment. Methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) concentrations in meconium did not predict infant birth parameters or NAS severity. Prospective urine testing defined meconium drug detection windows for opiates and cocaine as 3 months, rather than the currently accepted 6 months. The presence of opioids in meconium could be used as a biomarker for infants at elevated risk in the newborn period. Gray TR, Choo RE, Concheiro M, Williams E, Elko A, Jansson LM, Jones HE, Huestis MA. Prenatal methadone exposure, meconium biomarker concentrations and neonatal abstinence syndrome. *Addiction.* 2010 Dec; 105(12): 2151-2159.

Plasticity of Human Maternal Brain During the Early Postpartum Period

Animal studies suggest that structural changes occur in the maternal brain during the early postpartum period in regions such as the hypothalamus, amygdala, parietal lobe, and prefrontal cortex and such changes are related to the expression of maternal behaviors. In an attempt to explore this in humans, Dr. Linda Mayes and colleagues conducted a prospective longitudinal study to examine gray matter changes using voxel-based morphometry on high resolution magnetic resonance images of mothers' brains at two time points: 2-4 weeks postpartum and 3-4 months postpartum. Comparing gray matter volumes across these two time points, Dr. Linda Mayes and colleagues found increases in gray matter volume of the prefrontal cortex, parietal lobes, and midbrain areas. Increased gray matter volume in the midbrain including the hypothalamus, substantia nigra, and amygdala was associated with maternal positive perception of her baby. These results suggest that the first months of motherhood in humans are accompanied by structural changes in brain regions implicated in maternal motivation and behaviors. Kim P, Leckman JF, Mayes LC, Feldman R, Wang X, Swain JE. The Plasticity of human maternal brain: Longitudinal changes in brain anatomy during the early postpartum period. *Behav Neurosci.* 2010 Oct; 124(5): 695-700.

Small for Gestational Age and Higher Birth Weight Predict Childhood Obesity in Preterm Infants

Researchers from the Maternal Lifestyle Study (MLS) sought to determine the association between small for gestational age (SGA), birth weight, and childhood obesity within preterm polysubstance exposed children. The team sampled 312 preterm children with 11-year body mass index (BMI; age- and sex-specific) data from the MLS (51% girls, 21.5% SGA, 46% prenatal cocaine, and 55% tobacco exposed). Multinomial regression analyzed the association between 11-year obesity (OBE) and overweight (OW) and SGA, birth weight, first-year growth velocity, diet, and physical activity variables. Overall, 24% were obese (OB) (BMI for age ³95th percentile) and 16.7% were overweight (OW) (BMI ³85th and <95th percentiles). In adjusted analyses, SGA was associated with OW. Higher birth weight, growth velocity, and low exercise were associated with OBE and OW. There was no effect of substance exposure on obesity outcomes. Many (41%) of these high-risk preterm 11-year-olds were obese/overweight. Multiple growth-related processes may be involved in obesity risk for preterm children, including fetal programming as indicated by SGA effect. Gaskins RB, LaGasse LL, Liu J, Shankaran S, Lester BM, Bada HS, Bauer CR, Das A, Higgins RD, Roberts M. Small for gestational age and higher birth weight predict childhood obesity in preterm infants. *Am J Perinatol.* 2010 Oct; 27(9): 721-730.

Parental Depressive Symptoms and Adopted Toddler Behavior Problems

This study examined the developmental cascade of both genetic and environmental influences on toddlers' behavior problems through the longitudinal and multigenerational assessment of psychosocial risk. Dr. Jenae Neiderhiser and colleagues used data from the Early Growth and Development Study, a prospective adoption study, to test the intergenerational transmission of risk through the assessment of adoptive mother, adoptive father, and biological parent depressive symptoms on toddler behavior problems. Given that depression is often chronic, the team controlled for across-time continuity and found that in addition to associations between adoptive mother depressive symptoms and toddler externalizing problems, adoptive father depressive symptoms when the child is 9 months of age were associated with toddler problems and associated with maternal depressive symptoms. Findings also indicated that a genetic effect may indirectly influence toddler problems through prenatal pregnancy risk. These findings help to describe how multiple generations are linked through genetic (biological parent), timing

(developmental age of the child), and contextual (marital partner) pathways. Pemberton CK, Neiderhiser JM, Leve LD, Natsuaki MN, Shaw DS, Reiss D, Ge X. Influence of parental depressive symptoms on adopted toddler behaviors: An emerging developmental cascade of genetic and environmental effects. *Dev Psychopathol.* 2010 Nov; 22(4): 803-818.

Validity of Recall of Tobacco Use in Two Prospective Cohorts

This project studied the convergent validity of current recall of tobacco-related health behaviors, compared with prospective self-report collected earlier at two sites. Cohorts were from the Oregon Research Institute at Eugene (N = 346, collected 19.5 years earlier) and the University of Pittsburgh, Pennsylvania (N = 294, collected 3.9 years earlier). Current recall was examined through computer-assisted interviews with the Lifetime Tobacco Use Questionnaire from 2005 through 2008. Convergent validity estimates demonstrated variability. Validity estimates of some tobacco use measures were significant for Oregon subjects (age at first cigarette, number of cigarettes/day, quit attempts yes/no and number of attempts, and abstinence symptoms at quitting). Validity estimates of Pittsburgh subjects' self-reports of tobacco use and abstinence symptoms were significant for all tobacco use and abstinence symptoms and for responses to initial use of tobacco. These findings support the utility of collecting recalled self-report information for reconstructing salient lifetime health behaviors and underscore the need for careful interpretation. Brigham J, Lessov-Schlaggar CN, Javitz HS, Krasnow RE, Tildesley E, Andrews J, Hops H, Cornelius MD, Day NL, McElroy M, Swan GE. Validity of recall of tobacco use in two prospective cohorts. *Am J Epidemiol.* 2010 Oct 1; 172(7): 828-835.

Reducing Drug Use, HIV Risk, and Recidivism among Young Men Leaving Jail

Dr. Nicholas Freudenberg and his colleagues conducted an assessment of REAL MEN (Returning Educated African-American and Latino Men to Enriched Neighborhoods), an intervention designed to reduce drug use, risky sexual behavior and criminal activity among 16-18-year-old males leaving New York City jails. Participants (N = 552) were recruited in city jails and randomly assigned to receive an intensive 30-hour jail/community-based intervention or a single jail-based discharge planning session. All participants were also referred to optional services at a community-based organization (CBO). One year after release from jail, 397 (72%) participants completed a follow-up interview. Logistic and ordinary least squares regression was used to evaluate the impact of the intervention on drug use, risky sexual behavior, criminal justice involvement, and school/work involvement post release. Assignment to REAL MEN and, independently, use of CBO services, significantly reduced the odds of substance dependence 1 year after release. Those assigned to the intervention spent 29 fewer days in jail compared with the comparison group. Compared to non-CBO visitors, those who visited the CBO were more likely to have attended school or found work in the year after release. Jail and community services reduced drug dependence 1 year after release and the number of days spent in jail after the index arrest. While these findings suggest that multifaceted interventions can improve outcomes for young men leaving jail, rates of drug use, risky sexual behavior, and recidivism remained high for all participants after release from jail, suggesting the need for additional policy and programmatic interventions. Freudenberg N, Ramaswamy M, Daniels J, Crum M, Ompad DC, Vlahov D. Reducing drug use, human immunodeficiency virus risk, and recidivism among young men leaving jail: evaluation of the REAL MEN re-entry program. *J Adolesc Health.* 2010 Nov; 47(5): 448-455.



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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Clinical Neuroscience Research

OPRM1 Gene Variants Modulate Amphetamine-Induced Euphoria in Humans

Drs. Hamidovic, de Wit and colleagues at the University of Chicago sought to determine the subjective response to amphetamine in relation to genetic polymorphisms and haplotypes of the mu-opioid receptor. Choosing two previously recognized SNPs (and related haplotypes) in the OPRM1 gene because several lines of evidence suggest that endogenous opioid contributes to the rewarding effects of stimulant drugs, 0, 10, and 20 mg doses of amphetamine were administered and levels of Euphoria, Energy, and Stimulation were self-reported on a questionnaire. The results showed that two of the SNPs and two of the haplotypes were related to the effects seen with the 10mg dose suggesting that genetic variability in the mu-opioid receptor gene influences the subjective effect of amphetamine. Dlugos AM, Hamidovic A, Hodgkinson C, Shen PH, Goldman D, Palmer AA, de Wit H. OPRM1 gene variants modulate amphetamine-induced euphoria in humans. *Genes, Brain and Behavior*. 2010. [Epub ahead of print].

Loss of Laterality of Motor Performance in Chronic Cocaine Users

Drs. Hanlon, Porrino and colleagues at Wake Forest investigated the effect of chronic cocaine use on motor performance. Using a motor sequencing task (viewing and copying sequential finger movements) while measuring fMRI (BOLD), subjects that did not use cocaine had large (expected) activations of motor control centers in the left hemisphere which were significantly larger than in the right hemisphere. While cocaine users also had higher activation in the left hemisphere, the asymmetry compared to the right was significantly reduced. The results demonstrate that there are pronounced alterations in sensorimotor control in cocaine-using individuals which are associated with functional alterations throughout movement-related neural networks. Hanlon CA, Wesley MJ, Roth AJ, Miller MD, Porrino LJ. Loss of laterality in chronic cocaine users: an fMRI investigation of sensorimotor control. *Psychiat Res Neuroimaging*. 2010; 181: 15-23.

A C17T Polymorphism in the Mu Opiate Receptor is Associated with Quantitative Measures of Drug Use in African American Women

Dr. Kreek and colleagues at Rockefeller University used an established database of HIV and non-HIV individuals to determine genetic associations with drug use reported in repeated visits. A quantitative assessment instrument was used over several visits to compare gene variants with drug use as a

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continuous variable. Drug use scores were higher for cocaine, alcohol, and tobacco (but not opiates where prevalence in this sample was low) in African American women with the TT genotype of the OPRM1 gene. Crystal HA, Hamon S, Randesi M, Cook J, Anastos K, Lazar J, Liu C, Pearce L, Golub E, Valcour V, Weber KM, Holman S, Ho A, Kreek MJ. A C17T polymorphism in the mu opiate receptor is associated with quantitative measures of drug use in African American women. *Addiction Biol.* 2010. [doi:10.1111/j.1369-1600.2010.00265.x Epub ahead of print].

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Methylphenidate Improves Inhibitory Control Correlated with Activation of Specific Brain Regions in Cocaine-Dependent Patients

Drs. Malison, Li, Morgan and colleagues at Yale University School of Medicine assessed stop signal reaction time as a measure of inhibitory control in cocaine-dependent patients and its modulation by intravenous methylphenidate. Compared to placebo, reaction time was improved and the improvement was positively correlated with activation of the left middle frontal cortex and negatively correlated with activation of the ventromedial prefrontal cortex. These results implicate a specific neural mechanism whereby stimulants improve inhibitory control and thus suggest targets for treatment. Li C-SR, Morgan PT, Matuskey D, Abdelghany O, Luo X, Chang JLK, Rounsaville BJ, Ding Y-S, Malison RT. Biological markers of the effects of intravenous methylphenidate improving inhibitory control in cocaine-dependent patients. *PNAS.* 2010 August; 107(32): 14455-14459.

Compromised White Matter Integrity Was Related to Decision Making in Patients with Cocaine Dependence

Drs. Moeller, Lane and colleagues at the University of Texas Health Science Center (Houston) assessed cocaine dependent and healthy subjects with a voxel-wise analysis (Tract Based Spatial Statistics) of diffusion tensor imaging and compared white matter integrity to performance on a decision-making task (Iowa Gambling Task). Results demonstrated deficits in white matter integrity in several tracts including the superior longitudinal fasciculus, corticospinal tract, and superior corona radiata in cocaine patients who were also deficient in decision-making. These results suggest a functional relationship between these fiber tracts and cognitive performance. Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, Narayana PA, Moeller FG. Diffusion tensor imaging and decision making in cocaine dependence. *PLoS ONE* 2010 5(7): 1-9.

Individual and Additive Effects of the CNR1 and FAAH Genes on Brain Response to Marijuana Cues

Drs. Filbey, Hutchison and colleagues at the Mind Research Network compared heavy marijuana users who carried the C allele of CNR1 (vs. A/A) (which codes for the cannabinoid (CB1) receptor) to users who had the C/C genotype of a fatty acid amide hydrolase (FAAH) gene which inactivates anandamide, an endogenous CB1 agonist. Those with the C allele of CNR1 and C/C of FAAH had greater activation, assessed by fMRI, to marijuana cues in the orbitofrontal cortex and anterior cingulate gyrus. In addition, those with the FAAH C/C genotype also had greater activation in the nucleus accumbens. These results suggest that these genotypes may enhance neural response in reward areas to marijuana cues. Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE. Individual and additive effects of the CNR1 and FAAH genes on brain response to marijuana cues. *Neuropsychopharm.* 2010; 35: 967-975.

Brain Glutamate Level as an Early Surrogate Marker for Monitoring HIV Severity and Treatment Effects

Dr. Chang and associates at the University of Hawaii measured glutamate concentrations in the basal ganglia, frontal gray and white matter, and parietal gray matter of HIV+ and age-and-education-matched HIV- subjects using echo-time averaged proton magnetic resonance spectroscopy. The results showed that HIV subjects with cognitive deficits had lower glutamate in the parietal gray matter, while those without cognitive deficits tended to show higher basal ganglia glutamate. Lower parietal and frontal gray matter glutamate was associated with a greater number of nucleoside reverse transcriptase inhibitors, which was predictive of poorer cognitive performance. Correlations between glutamate and cognitive performance, but not the other findings, remained significant after correction for multiple comparisons. It was concluded that the proton magnetic resonance spectroscopy measurement of brain glutamate may provide an early surrogate marker for monitoring disease severity and treatment effects. Ernst T, Jiang CS, Nakama H, Buchthal S, Chang L. Lower brain glutamate is associated with cognitive deficits in HIV patients: a new mechanism for HIV-associated neurocognitive disorder. *J Magn Reson Imaging*. 2010 Nov; 32(5): 1045-1053.

Genotypic Variability Underlying Individual Vulnerability to the Neurotoxic Effects of Methamphetamine

Drs. Cherner, Grant and colleagues at the University of California, San Diego evaluated individual differences in deficits of neuropsychological performance among methamphetamine addicts, and compared them with genotypic variability in metabolic clearance of methamphetamine. Results showed that individuals with higher activity of cytochrome P450-2D6 (CYP2D6) had worse overall neuropsychological performance, but not scores on mood disorder. These individuals were three times as likely to be cognitively impaired in comparison to individuals who had intermediate or low activity of methamphetamine metabolism. The study suggests that more efficient metabolism of methamphetamine was associated with worse neurocognitive outcomes in humans and supports the hypothesis that the products of oxidative metabolism of methamphetamine may be a possible cause of brain injury. The data may explain the observation that some methamphetamine users develop neuropsychological impairments while others with similar drug exposure do not; and that vulnerability is often unrelated to methamphetamine exposure parameters such as lifetime consumption or length of abstinence. Cherner M, Bousman C, Everall I, Barron D, Letendre S, Vaida F, Atkinson JH, Heaton R, Grant I; HNRC Group. Cytochrome P450-2D6 extensive metabolizers are more vulnerable to methamphetamine-associated neurocognitive impairment: Preliminary findings. *J Int Neuropsychol Soc*. 2010 16(5): 890-901.

Gender Different Performance Patterns on Procedural Learning Tasks in HIV+ Individuals

Dr. Martin and colleagues at the University of Illinois College of Medicine measured motor skill and probabilistic learning, tasks with a non-declarative or procedural learning component that are dependent on integrity of prefrontal-striatal systems, in well-matched groups of individuals with a history of substance dependence and with or without HIV+ status. All participants were abstinent at testing. Compared to HIV- women, HIV+ women performed significantly more poorly on both tasks, but HIV+ men's performance did not differ significantly from that of HIV- men on either task. These different patterns of performance indicate that features of HIV-associated neurocognitive disorder (HAND) cannot always be generalized from men to women. Additional studies are warranted to address directly the possibility of sex differences in HAND and the possibility that women may be more vulnerable to the effects of HIV and substance dependence in some neurocognitive domains. Martin E,

Gonzalez R, Vassileva J, Maki P. HIV+ men and women show different performance patterns on procedural learning tasks. *J Clin Exp Neuropsychol*. 2010 Aug; 5: 1-9.

Measures of Learning, Memory and Processing Speed Accurately Predict Smoking Status in Short-Term Abstinent Treatment-Seeking Alcohol-Dependent Individuals

Dr. Durazzo and colleagues at the Center for Imaging of Neurodegenerative Diseases of the San Francisco VA Medical Center determined which measures commonly used to assess neurocognition in individuals with alcohol use disorders accurately predict the smoking status of those seeking treatment for alcohol dependence. Measures of processing speed, learning and memory robustly predicted the smoking status of alcohol-dependent individuals with high sensitivity and specificity during early abstinence. The results also identified specific measures within a comprehensive neurocognitive battery that discriminated smoking and non-smoking alcohol-dependent individuals with a high sensitivity and specificity. The association of greater smoking chronicity and poorer performance on multiple measures after control for alcohol consumption suggest that chronic smoking adds an additional burden to neurocognitive function for those with alcohol dependence. Durazzo TC, Fryer SL, Rothlind JC, Vertinski M, Gazdzinski S, Mon A, Meyerhoff DJ. Measures of learning, memory and processing speed accurately predict smoking status in short-term abstinent treatment-seeking alcohol-dependent individuals. *Alcohol*. 2010 Nov-Dec; 45(6): 507-513.

Prediction of Individual Brain Maturity Using fMRI

Dr. Lessov-Schlaggar and colleagues at Washington University School of Medicine showed that vector machine-based multivariate pattern analysis extracts sufficient information from resting state functional connectivity MRI (fcMRI) data to make accurate predictions about individuals' brain maturity across development. Only 5 minutes of resting-state fcMRI data from 238 scans of typically developing volunteers (ages 7 to 30 years) was needed to provide a measure of individual brain maturity that was termed functional connectivity maturation index. The resultant functional maturation curve accounted for 55% of the sample variance and followed a nonlinear asymptotic growth curve shape. The greatest relative contribution to predicting individual brain maturity was made by the weakening of short-range functional connections between the adult brain's major functional networks. Dosenbach NU, Nardos B, Cohen AL, Fair DA, Power JD, Church JA, Nelson SM, Wig GS, Vogel AC, Lessov-Schlaggar CN, Barnes KA, Dubis JW, Feczko E, Coalson RS, Pruett JR Jr, Barch DM, Petersen SE, Schlaggar BL. Prediction of individual brain maturity using fMRI. *Science*. 2010 Sep 10; 329(5997): 1358-1361. Erratum in: *Science*. 2010 Nov 5; 330(6005): 756.

Smoking Withdrawal Shifts the Spatiotemporal Dynamics of Neurocognition

Dr. McClernon and colleagues at Duke University Medical Center used functional magnetic resonance imaging scans to localize brain activation changes in adult smokers following smoking-as-usual and after 24-hours abstinence. Smoking withdrawal is associated with significant deficits in the ability to initiate and maintain attention for extended periods of time (i.e., sustained attention, SA). Compared to smoking-as-usual, 24-hour abstinence resulted in decreased sustained activation in the right inferior and middle frontal gyri but increased transient activation across dispersed cortical areas including the precuneus and right superior frontal gyrus. Greater task difficulty was associated with even greater transient activation during abstinence in

mostly right hemisphere regions including the right inferior frontal gyrus. These findings suggest smoking withdrawal shifts the temporal and spatial dynamics of neurocognition from sustained, right prefrontal activation reflecting proactive cognitive control to more dispersed and transient activation reflecting reactive control. Kozink RV, Lutz AM, Rose JE, Froeliger B, McClernon FJ. Smoking withdrawal shifts the spatiotemporal dynamics of neurocognition. *Addict Biol.* 2010 Oct; 15(4): 480-490.

Impulsivity is Related to Regional Differences Dopamine in Humans

Dr. Zald and colleagues at Vanderbilt University used PET ligand imaging of DA signaling to assess differences in impulsive traits in healthy human volunteers. Using PET scans with the D2/D3 ligand [18F]fallypride, higher levels of trait impulsivity were associated with diminished midbrain D2/D3 autoreceptor binding and greater amphetamine-induced DA release in the striatum, which was in turn associated with stimulant craving. Path analysis confirmed that the impact of decreased midbrain D2/D3 autoreceptor availability on trait impulsivity is mediated in part through its effect on stimulated striatal DA release. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH. Dopaminergic network differences in human impulsivity. *Science* 2010 Jul; 329(5991): 532.

Parkinson's Disease among Methamphetamine Users

Dr. Kish and colleagues at the University of Toronto conducted a population-based cohort study based on statewide inpatient hospital discharges to explore the association of methamphetamine use on the incidence of Parkinson's Disease. The rationale for the study was the observation that methamphetamine exposure in experimental animals can damage brain dopamine neurons, suggesting that people with methamphetamine-related disorders might have greater risk of subsequent admission with a Parkinson's disease diagnosis. Individuals with reported methamphetamine-related conditions (n = 1,863) were matched on demographic variables and follow-up time with those with primary appendicitis conditions (n = 9,315). The methamphetamine group showed increased risk of a subsequent admission with Parkinson's disease compared to the matched appendicitis group (adjusted hazard ratio = 2.65; Cox Regression). While provocative, the authors emphasize that these results are highly preliminary and should be interpreted cautiously due to an uncertainty regarding diagnostic validity and a small number of incident cases with suspected Parkinson's disease. Nevertheless, these data provide some evidence that methamphetamine users might be at greater than normal risk for developing Parkinson's disease. Callaghan RC, Cunningham JK, Sajeev G, Kish SJ. Incidence of Parkinson's disease among hospital patients with methamphetamine-use disorders. *Mov. Disord* 2010 Oct; 25(14): 2333-2339.

Smoking-Induced Occupancy of 2-Nicotinic Acetylcholine Receptors

Dr. Cosgrove and colleagues at Yale University School of Medicine used an improved method to estimate non-specific binding using SPECT. Beta(2) nicotinic receptor ligand I-123-5-IA was used to quantify high-affinity nicotinic acetylcholine receptors in human SPECT scans. Eleven nicotine-dependent subjects abstained from tobacco smoke for a week prior to the SPECT scan session. At approximately 6 h after the start of the infusion, three 30-min SPECT scans and a 15-min transmission-emission scan were acquired to obtain baseline beta 2*-nAChR availability. Subjects then smoked to satiety; scans

showed receptor occupancy was 67%. In the thalamus, 20% of the total binding was non-displaceable. These results are in agreement with previous findings and suggest that when satiating doses of nicotine are administered to smokers, imaging of receptor availability can yield valuable data, such as quantifiable measures of non-displaceable binding. Esterlis I, Cosgrove KP, Batis JC, Bois F, Stiklus SM, Perkins E, Seibyl JP, Carson RE, Staley JK. Quantification of smoking-induced occupancy of 2-nicotinic acetylcholine receptors: estimation of non-displaceable binding. *J Nucl Med* 2010; 51(8): 1226-1233.

Clinically Relevant Doses of Methylphenidate Significantly Occupy Human Norepinephrine Transporters

Dr. Ding and colleagues at Yale University School of Medicine used PET ligand imaging with (S,S)-[¹¹C] methylreboxetine ([¹¹C]MRB) to determine the occupancy of the brain norepinephrine transporter by methylphenidate in vivo in humans. In vitro, the affinity of methylphenidate for the norepinephrine transporter (NET) is higher than that for the dopamine transporter (DAT). Binding potential, non-displaceable (BP(ND)) was reduced by methylphenidate in a dose-dependent manner in the thalamus and other NET-rich regions. These results indicate that the average clinical maintenance dose of methylphenidate (.35-.55 mg/kg) produces 70% to 80% occupancy of NET. Furthermore, the ED₅₀ is lower than that for DAT (.25 mg/kg), suggesting the potential relevance of NET blockade. Hannestad J, Gallezot J, Planeta-Wilson B, Lin S, Williams WA, van Dyck CH, Malison RT, Carson RE, Ding Y-S. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol. Psychiatry* 2010 Nov; 68(9): 854-860.

Verbal Learning and Memory Deficits in Nondependent Stimulant Use

Dr. Paulus and colleagues at the University of California, San Diego, studied whether subtle learning and memory problems characterize individuals who exhibit occasional but not chronic use of stimulants. One hundred fifty-four young (age 18-25), occasional, nondependent stimulant users and 48 stimulant-naive comparison subjects performed the California Verbal Learning Test II. Compared with stimulant-naive subjects, occasional stimulant users showed significant performance deficits, most pronounced in the verbal recall and recognition domains. The type of stimulant used was of major relevance: users of cocaine only were less impaired, whereas cumulative use of prescription stimulants (e.g. amphetamines and methylphenidate) was associated with impaired verbal learning and memory capacities. It is possible that subtle and possibly pre-existing neurocognitive deficiencies in occasional users of stimulants underlie the use of these drugs, especially for studying and cognitive enhancement. Critically, despite beneficial short-term effects, cumulative use, particularly of prescription amphetamines and methylphenidate, intensifies these deficits. Reske M, Eidt CA, Delis DC, Paulus MP. Nondependent stimulant users of cocaine and prescription amphetamines show verbal learning and memory deficits. *Biol. Psychiatry* 2010; 68(8): 762-769.

Oral Methylphenidate Normalizes Cingulate Activity in Cocaine Addiction During a Salient Cognitive Task

Dr. Goldstein and colleagues at Brookhaven National Laboratories used functional MRI to test the hypothesis that oral methylphenidate (MPH) will alleviate brain hypoactivity and improve associated performance during cognitive tasks in individuals with cocaine-use disorders. MPH has been shown to improve treatment outcome for cocaine addiction in clinical trials, but has

been found to normalize cortical function and improve associated cognitive abilities in other frontal lobe pathologies. Results in cocaine users demonstrated increased responses to a rewarded drug cue-reactivity task in both major subdivisions of the anterior cingulate cortex (including the caudal-dorsal and rostroventromedial areas extending to the medial orbitofrontal cortex). These fMRI results were associated with reduced errors of commission (a common impulsivity measure) and improved task accuracy, especially during the drug (vs. neutral) cue-reactivity condition in all subjects. These results indicate that MPH can improve brain and cognitive performance in cocaine abusers in controlled settings; however the clinical utility of such MPH-induced brain-behavior enhancements remains to be tested. Goldstein RZ, Woicik PA, Maloney T, Tomasi D, Alia-Klein N, Shan J, Honorio J, Samaras D, Wang R, Telang F, Wang G, Volkow ND. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. PNAS. USA 2010; 107(38): 16667-16672.

Neural Substrates of Attentional Bias for Smoking-Related Cues

Dr. Janes and colleagues at McLean Hospital examined the relationship between implicit attentional bias for drug-related stimuli, as measured by emotional Stroop tasks, and cue-related brain activity. Positive correlations were found between attentional bias and reactivity to smoking images in brain areas including the amygdala, hippocampus, parahippocampal gyrus, insula, and occipital cortex which are involved in emotion, memory, introspection, and visual processing,. These findings suggest that smokers with elevated attentional biases to smoking-related stimuli may more readily shift attention away from other external stimuli and toward smoking stimuli-induced internal states and emotional memories. Such attentional shifts may contribute to increased interference by smoking cues, possibly increasing relapse vulnerability. Treatments capable of inhibiting shifts to drug cue-induced memories and internal states may lead to personalized tobacco dependence treatment for smokers with high attentional bias to smoking-related stimuli. Janes AC, Pizzagalli DA, Richardt S, Frederick BDB, Holmes AJ, Sousa J, Fava M, Evins AE, Kaufman MJ. Neural substrates of attentional bias for smoking-related cues: An fMRI study. Neuropsychopharm 2010 Nov; 35(12): 2339-2345.

A Virtual Reality-Based fMRI Study of Reward-Based Spatial Learning

Dr. Martinez and colleagues at Columbia University used fMRI to characterize the neural correlates of reward-based spatial learning in humans. The study design used virtual reality with fMRI to measure differential contributions of the hippocampus and other temporo-parietal areas to searching and reward processing during reward-based spatial (maze-learning) task. Results showed activation of temporo-parietal regions, but not including the hippocampus. However, the receipt of rewards associated with activation of the hippocampus in a control condition when using the extra-maze cues for navigation was rendered impossible by randomizing the spatial location of cues. This translational research will permit parallel studies in animals and humans to establish the functional similarity of learning systems across species; cellular and molecular studies in animals may then inform the effects of manipulations on these systems in humans, and fMRI studies in humans may inform the interpretation and relevance of findings in animals. Marsh R, Hao X, Xu D, Wang Z, Duan Y, Liu J, Kangarlou A, Martinez D, Garcia F, Tau GZ. A virtual reality-based fMRI study of reward-based spatial learning. Neuropsychologia 2010; 48(10): 2912-2921.

Associations of Anterior Insula Activity with Message Framing and

Decision Making

Dr. Brown and colleagues at the University of Illinois used fMRI to study the neural mechanisms underlying the influence of persuasive messages on decision making. Specifically, this study examined brain activity associated with how informative messages alter risk appraisal during choice. Healthy subjects performed the Iowa Gambling Task while viewing a positively framed, negatively framed, or control message about the options. The right anterior insula correlated with improvement in choice behavior due to the positively framed but not the negatively framed message. With the positively framed message, there was increased activation proportional to message effectiveness when less-preferred options were chosen, consistent with a role in the prediction of adverse outcomes. In addition, the dorsomedial and the left dorsolateral prefrontal cortex correlated with overall decision quality, regardless of message type. The dorsomedial region mediated the relationship between the right anterior insula and decision quality with the positively framed messages. These findings suggest a network of frontal brain regions that integrate informative messages into the evaluation of options during decision making. These results advance our understanding of how brain processes influence how drug and other health messages change behavior. Krawitz A, Fukunaga R, Brown JW. Anterior insula activity predicts the influence of positively framed messages on decision making. *Cogn Affect Behav Neurosci*. 2010; 10(3): 392-405.

A Contingent Attentional Capture Paradigm Reveals Involuntary Transfer of a Top-Down Attentional Set into the Focus of Attention

Dr. Weissman and colleagues at Northwestern University tested the cognitive processes during contingent attentional capture which occurs when involuntary direction of attention to a distracter leads to a limited-capacity focus of attention onto a subsequent target with the same stimulus features. Contingent attentional capture effects in healthy human participants from a target-colored distracter were only one half to one third as large when subsequent target identification relied on the same (vs. a different) attentional set. Subsequent experiments ruled out bottom-up perceptual priming of the distracter's color and a feature-based interference as an alternative account of the findings. Thus, capacity limitations in working memory strongly influence contingent attentional capture when multiple attentional sets guide selection. This phenomenon may be part of the process that leads drug abusers to be inappropriately attentive to drug-related stimuli. Moore KS, Weissman DH. Involuntary transfer of a top-down attentional set into the focus of attention: Evidence from a contingent attentional capture paradigm. *Atten Percept Psychophys*. 2010 Aug; 72(6): 1495-1509.

Functional Heterogeneity of Cognitive Effects within Medial Prefrontal Cortex

Dr. Brown and colleagues at the University of Illinois used fMRI to simultaneously contrast multiple effects of error, conflict, and task-switching that have been proposed as functions of the medial prefrontal cortex. Studies of the medial prefrontal cortex (mPFC) function with a particular focus on the anterior cingulate cortex have led to a variety of functional interpretations including conflict detection, error likelihood prediction, volatility monitoring, and several distinct theories of error detection. Arguments for and against particular theories often treat mPFC as functionally homogeneous, or at least nearly so, despite some evidence for distinct functional sub-regions. In this study, overlapping yet functionally distinct sub-regions of mPFC, with activations related to dominant error, conflict, and task-switching effects were successively found along a rostral-ventral to caudal-dorsal gradient within

medial prefrontal cortex. Activations in the rostral cingulate zone were strongly correlated with the unexpectedness of outcomes, suggesting a role in outcome prediction and preparing control systems to deal with anticipated outcomes. The results as a whole support a resolution of some ongoing debates regarding functions of corresponding distinct yet overlapping sub-regions of mPFC. More precise characterization of the functional heterogeneity of this brain region is critical to the interpretations of brain activity found in various subregions of the mPFC in drug abusers. Nee DE, Kastner S, Brown JW. Functional heterogeneity of conflict, error, task-switching, and unexpectedness effects within medial prefrontal cortex. *Neuroimage* 2011 Jan; 54(1): 528-540.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Epidemiology and Etiology Research

Association of Highly Active Antiretroviral Therapy Coverage, Population Viral Load, and Yearly New HIV Diagnoses in British Columbia, Canada: A Population-Based Study

Results of cohort studies and mathematical models have suggested that increased coverage with highly active antiretroviral therapy (HAART) could reduce HIV transmission. Researchers aimed to estimate the association between plasma HIV-1 viral load, HAART coverage, and number of new cases of HIV in the population of a Canadian province. They undertook a population-based study of HAART coverage and HIV transmission in British Columbia, Canada. Data for number of HIV tests done and new HIV diagnoses were obtained from the British Columbia Centre for Disease Control. Data for viral load, CD4 cell count, and HAART use were extracted from the British Columbia Centre for Excellence in HIV/AIDS population-based registries. Trends of new HIV-positive tests and numbers of individuals on HAART were modeled using generalised additive models. Poisson log-linear regression models were used to estimate the association between new HIV diagnoses and viral load, year, and number of individuals on HAART. Between 1996 and 2009, the number of individuals receiving HAART increased from 837 to 5413 (547% increase; $p=0.002$), and the number of new HIV diagnoses fell from 702 to 338 per year (52% decrease; $p=0.001$). The overall correlation between number of individuals on HAART and number of individuals newly testing positive for HIV per year was -0.89 ($p<0.0001$). For every 100 additional individuals on HAART, the number of new HIV cases decreased by a factor of 0.97 (95% CI 0.96-0.98), and per 1 log(10) decrease in viral load, the number of new HIV cases decreased by a factor of 0.86 (0.75-0.98). These findings demonstrate a strong population-level association between increasing HAART coverage, decreased viral load, and decreased number of new HIV diagnoses per year. The results also provide support of the secondary benefits of HAART now gaining recognition as part of existing medical guidelines to reduce HIV transmission. Montaner J, Lima V, Barrios R, Yip B, Wood E, Kerr T, Shannon K, Harrigan P, Hogg R, Daly P, Kendall P. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: A population-based study. *Lancet*. 2010; 376 (9740): 532-539.

Incorporating Age at Onset of Smoking into Genetic Models for Nicotine Dependence

Nicotine dependence is moderately heritable, but identified genetic associations explain only modest portions of this heritability. The authors hypothesized that incorporation of SNP-by-environment interaction into association analyses might bolster gene discovery efforts and prediction of nicotine dependence.

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They incorporated the interaction between allele count and age at onset of regular smoking (AOS) into association analyses of nicotine dependence. Subjects were from the Collaborative Genetic Study of Nicotine Dependence and included 797 cases ascertained for Fagerström nicotine dependence and 811 non-nicotine-dependent smokers as controls, all of European descent. They analyzed 3369 SNPs from 349 candidate genes. Compared with main effect models, SNP x AOS interaction models resulted in higher numbers of nominally significant tests, increased predictive utility at individual SNPs and higher predictive utility in a multi-locus model. Some SNPs previously documented in main effect analyses exhibited improved fits in the joint analysis, including rs16969968 from *CHRNA5* and rs2314379 from *MAP3K4*. *CHRNA5* exhibited larger effects in later-onset smokers, in contrast with a previous report that suggested the opposite interaction. In addition, a number of SNPs that did not emerge in main effect analyses were among the strongest findings in the interaction analyses. These include SNPs located in *GRIN2B* ($P = 1.5 \times 10^{-5}$), which encodes a subunit of the N-methyl-D-aspartate receptor channel, a key molecule in mediating age-dependent synaptic plasticity. These findings are important in suggesting that incorporation of logically chosen interaction parameters, such as AOS, into genetic models of substance use disorders may increase the degree of explained phenotypic variation and constitutes a promising avenue for gene discovery. Gruzca R, Johnson E, Krueger R, Breslau N, Saccone N, Chen L, Derringer J, Agrawal A, Lynskey M, Bierut L. Incorporating age at onset of smoking into genetic models for nicotine dependence: evidence for interaction with multiple genes. *Addict Biol.* 2010; 15 (3): 346-357.

[Publications](#)[Staff Highlights](#)[Grantee Honors](#)

The Effects of Maternal Smoking During Pregnancy on Offspring Outcomes

This study sought to evaluate the possible association between maternal smoking during pregnancy and offspring outcomes of birth weight, pre-term birth, remediation, low scholastic achievement, regular smoking, attention deficit hyperactivity disorder and conduct problems while controlling for similar behaviors in parents. Using telephone interviews, data were collected, in 2001 and 2004, as a part of two United States offspring-of-twins projects. Fathers, who were twins participating in the Vietnam Era Twin Registry, their female spouse and their offspring were interviewed, and information on 1,342 unique pregnancies in mothers with a history of regular smoking was utilized for these analyses. The association between maternal smoking during pregnancy and birth weight, pre-term birth, remediation, low scholastic achievement, regular smoking, attention deficit hyperactivity disorder and conduct disorder while controlling for similar behaviors in parents, was examined using regression. Maternal smoking during pregnancy was associated with decreased birth weight, low scholastic achievement, regular smoking and attention deficit hyperactivity disorder. However, the association between maternal smoking during pregnancy and offspring attention deficit hyperactivity disorder was explained by maternal attention deficit hyperactivity disorder. Maternal smoking during pregnancy was also associated with earlier age of offspring initiation of smoking and onset of regular smoking. The authors conclude that maternal smoking during pregnancy may influence certain offspring outcomes via mechanisms that are independent from genetic risk attributable to comorbid conditions and that assisting expecting mothers with their smoking cessation efforts will likely provide widespread health benefits to both mother and offspring. Applying genetic analyses to this important public health problem highlights the environmental importance of in utero exposure and points to potentially fruitful avenues for intervention. Agrawal A, Scherrer J, Grant J, Sartor C, Pergadia M, Duncan A, Madden P, Haber J, Jacob T, Bucholz K, Xian H. The effects of maternal smoking during pregnancy on offspring outcomes. *Prev Med.* 2009; 50 (1-2): 13-18.

Risk of Resistance to Highly Active Antiretroviral

Therapy among HIV-Positive Injecting Drug Users: A Meta-Analysis Although highly active antiretroviral therapy (HAART) is an effective treatment for HIV, many physicians withhold this treatment from HIV-positive injecting drug users (IDUs) because of fears of non-adherence and consequent development of antiretroviral resistance. Little is known, however, about whether the rates of resistance differ between IDUs and non-IDUs. Researchers conducted a meta-analysis of studies that compared HAART resistance rates in IDUs (current or previous) with those in HIV-positive patients infected by other routes and who had never injected drugs. They used a random-effects model to investigate overall resistance rates and resistance to individual drug classes. Of 181 potential studies, 27 were eligible for review. They were able to extract data from 14 studies, but excluded two (due to a very small sample size of IDUs or limited availability of study data), leaving 12 studies. The meta-analysis involved a total of 9055 patients, of which 2054 (23%) were IDUs. The risk of developing antiretroviral resistance did not differ significantly between IDU and non-IDU (odds ratio 1.04, 95% CI 0.74-1.45, $p=0.84$). Rates of loss to follow-up and virological failure were similar in IDU and non-IDU samples. The existing evidence does not support the common practice of withholding antiretroviral therapy from HIV-positive IDU out of concern over an elevated risk of antiretroviral resistance. Therapeutic guidelines should therefore consider reassessment of this important issue. Werb D, Mills E, Montaner J, Wood E. Risk of resistance to highly active antiretroviral therapy among HIV-positive injecting drug users: A meta-analysis. *Lancet Infect Dis.* 2010; 10 (7): 464-469.

PTSD Contributes to Teen and Young Adult Cannabis Use Disorders

Previous studies involving adults suggest that Post Traumatic Stress Disorder (PTSD) increases the prevalence of cannabis use disorders (CUD) (cannabis dependence and cannabis abuse). However, little work with PTSD and CUD has been conducted involving adolescents, despite the fact that CUD typically has their onset during adolescence. This study addresses the effect of PTSD on CUD among teenagers transitioning to young adulthood. The subjects in this ongoing study were the offspring of adult men with a lifetime history of a substance use disorder (SUD) (SUD+ probands, $N=343$) vs those with no lifetime history of a SUD (SUD-probands, $N=350$). The participants were initially recruited when the index sons of these fathers were 10-12 years of age, and subsequent assessments were conducted at age 12-14, 16, 19, 22, and 25. Other variables examined were an index of behavioral under control associated with future risk for developing SUD, known as the Transmissible Liability Index, or TLI, and affiliation with deviant peers. Multivariate logistic regression and path analyses were conducted. Of these 693 subjects, 31 subjects were diagnosed with PTSD, and 161 were diagnosed with a CUD. The CUD subjects included 136 male participants and 25 female participants, including 103 (64%) white participants and 58 (36%) participants of other races. Logistic regression demonstrated that the development of a CUD was significantly associated with deviance of peers, the TLI, African American race, PTSD, male gender, household SES (Wald=9.2, $p=0.002$), and being an offspring of a SUD+ proband. Path analyses demonstrated that PTSD is directly associated with the presence of a CUD and with peer deviance, that higher peer deviance is associated with the presence of a CUD, and that PTSD mediated the association between peer deviance and CUD. These findings suggest that PTSD contributes to the etiology of CUD among teenagers making the transition to young adulthood beyond the effects of deviant peers, other liability factors as measured on the TLI, and demographic factors. Cornelius J, Kirisci L, Reynolds M, Clark D, Hayes J, Tarter R. PTSD contributes to teen and young adult cannabis use disorders. *Addict Behav.* 2010; 35 (2): 91-94.

Accelerated Hepatitis B Vaccination Schedule among Drug Users: A Randomized Controlled Trial

Hepatitis B (HBV) vaccine provides a model for improving uptake and completion of multi-dose vaccinations in the drug-using community. The Drugs, AIDS, STDs, and Hepatitis (DASH) project conducted a randomized controlled trial among not-in-treatment current drug users in 2 urban neighborhoods. Neighborhoods were cluster-randomized to receive a standard behavioral intervention (which provided information on HIV) or an enhanced behavioral intervention (designed to increase acceptance of or adherence to the HBV vaccination protocol). Eligible participants (N=1260, 90% recent crack use, 30% IDU history) within clusters were randomized to a standard vaccination schedule (vaccines at 0, 1, and 6 months) or an accelerated vaccination schedule (vaccines at 0, 1, and 2 months). The outcomes were completion of the 3-dose vaccine and seroprotection against HBV. Of participants with negative screening results for HIV and HBV, 77% accepted HBV vaccination, and 75% of vaccinees received all 3 doses. IDUs on the accelerated schedule were significantly more likely to receive 3 doses (76%) than those on the standard schedule (66%; $P = .04$), although for drug users as a whole the corresponding adherence rates were 77% and 73%, respectively. No difference in adherence was observed between the behavioral intervention groups. Predictors of adherence were older age, African American race, stable housing, and alcohol use. Cumulative HBV seroprotection ($e10$ mIU/mL) was attained within 12 months by 65% of those completing the schedule, and seroprotection at 6 months was greater for those on the accelerated schedule. These findings demonstrate that the accelerated HBV vaccination schedule improves adherence among IDUs. Hwang L, Grimes C, Tran T, Clark A, Xia R, Lai D, Troisi C, Williams M. Accelerated Hepatitis B vaccination schedule among drug users: a randomized controlled trial. *J Infect Dis.* 2010; 202 (10): 1500-1509.

The Effect of Smoking on MAOA Promoter Methylation in DNA

Monoamine oxydase A (MAOA) plays a key role in modulating neurotransmission and possibly in nicotine dependence and other complex behavioral illnesses. Thus, understanding the genetics and epigenetics of MAOA may be helpful in understanding etiology and treatment of these disorders. Prior work by these authors using lymphoblast DNA prepared from 192 subjects from the Iowa Adoption Studies (IAS) demonstrated that decreased MAOA promoter methylation was associated with lifetime symptom count for nicotine dependence (ND) and provided suggestive evidence that the amount of methylation is genotype dependent. In the current investigation, the authors replicate and extend these prior findings in three ways using another 289 IAS subjects and the same methodologies. First, they found that methylation is dependent on current smoking status. Second, they introduced a factor analytic approach to DNA methylation, highlighting three distinct regions of the promoter that may function in somewhat different ways for males and females. Third, they directly compared the methylation signatures in DNA prepared from whole blood and lymphoblasts from a subset of these subjects and provide suggestive evidence favoring the use of lymphoblast DNA. The authors conclude that smoking reliably decreases MAOA methylation, but exact characterization of effects on level of methylation depend on genotype, smoking history, current smoking status, gender, and region examined. Philibert R, Beach S, Gunter T, Brody G, Madan A, Gerrard M. The effect of smoking on MAOA promoter methylation in DNA prepared from lymphoblasts and whole blood. *Am J Med Genet B Neuropsychiatr Genet.* 2010; 153B (2): 619-628.

Ongoing Drug Use and Outcomes from Highly Active Antiretroviral Therapy among Injection Drug Users in a Canadian Setting

The effect of ongoing illicit drug use on HIV treatment remains controversial, especially in countries where access to HIV treatment for active injection drug users (IDUs) is limited because of presumed non-adherence. Researchers sought to investigate the influence of drug use patterns on adherence to antiretroviral therapy and virological suppression among a community-recruited cohort of IDUs in Vancouver, Canada. They used generalized estimating equation logistic regression to explore the effect of abstinence versus ongoing drug use on adherence and virological suppression. A total of 381 HIV-positive IDUs were included in this analysis, among whom the median follow-up time was 30 months. In a multivariate model, no relationship was found between abstinence (reference) and active injection (adjusted odds ratio [AOR] 0.88, 95% confidence interval [CI] 0.65-1.17) and non-injection (AOR 0.97, 95% CI 0.67-1.41) drug use with adherence. In subanalyses, ongoing injection drug use was associated with a lower odds of virological suppression in comparison to abstinence (AOR 0.74, 95% CI 0.57-0.97; $P=0.026$) and both active IDUs and active non-IDUs had lower odds of virological suppression compared with abstinent participants when longer periods of virological suppression were considered. Lower rates of virological suppression associated with ongoing drug use were found, pointing to the importance of comprehensive systems of care and addiction treatment for active drug users. However, the absence of a strong relationship between abstinence and ongoing drug use and adherence among HIV-positive IDUs underscores the need to re-examine programs that limit antiretrovirals to abstinent individuals only. Krÿsi A, Milloy M, Kerr T, Zhang R, Guillemi S, Hogg R, Montaner J, Wood E. Ongoing drug use and outcomes from highly active antiretroviral therapy among injection drug users in a Canadian setting. *Antivir Ther.* 2010; 15 (5): 789-796.

Paternal Alcohol and Drug Dependence and Offspring Conduct Disorder: Gene-Environment Interplay

Not only are substance-use disorders and externalizing disorders frequently comorbid, they often co-occur in families across generations. The current study examined the role of genetic and environmental influences in the relationship between paternal histories of drug dependence or alcohol dependence and offspring conduct disorder using an offspring-of-twins design. Participants were male twins ($n = 1,774$) from the Vietnam Era Twin Registry, their offspring ($n = 1,917$), and mothers of the offspring ($n = 1,202$). Twins had a history of drug dependence, alcohol dependence, or neither. Based on the father's and his co-twin's drug-dependence or alcohol-dependence history and zygosity, risk groups were constructed to reflect different levels of genetic and environmental risk that were then used to predict offspring conduct disorder. After controlling for potentially confounding variables, the offspring of men with a history of drug dependence or alcohol dependence had significantly higher rates of conduct disorder, compared with offspring of men without this history. Offspring at higher genetic risk had higher rates of conduct disorder. High-risk offspring at lower environmental risk had lower rates of conduct disorder but only in the case of paternal drug-dependence risk. Lower environmental risk did not influence rates of offspring conduct disorder when the father had an alcohol-dependence history. The authors conclude that genetic risk associated with both paternal drug-dependence and paternal alcohol-dependence histories predicted offspring conduct-disorder risk, but only risk associated with paternal drug-dependence history was mitigated by having a low-risk environment. These results demonstrated a significant gene-environment interaction effect. Haber J, Bucholz K, Jacob T, Grant J, Scherrer J, Sartor C, Duncan A, Heath A. Effect of paternal alcohol and drug dependence on offspring conduct disorder: gene-environment interplay. *J Stud Alcohol Drugs.* 2010; 71 (5): 652-663.

Birth-Cohort Trends in Lifetime and Past-Year Prescription Opioid-Use Disorder Resulting from Nonmedical Use: Results from Two

National Surveys

The objective of this study was to test whether recent increases in the reported prevalence of opioid-use disorder in the United States occurred across all age groups (period effect), consistently only among younger age groups (age effect), or varied according to year of birth (cohort effects). The investigators analyzed data from the 1991-1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES) and the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), focusing on individuals ages 18-57, grouped by 10-year age intervals. Sample sizes for the present analyses were 30,846 for the NLAES and 31,397 for the NESARC. Prevalence of lifetime and past-year prescription opioid-use disorder resulting from nonmedical use (abuse and dependence) was examined. Within birth cohorts, prevalence of lifetime prescription opioid-use disorder increased during the 10 years between surveys, indicating the importance of age effects. In addition, lifetime and past-year prevalence of prescription opioid-use disorder was higher among more recent birth cohorts as compared with earlier birth cohorts, indicating the importance of cohort effects. Consistent with a period effect, cross-cohort comparisons showed that risk for prescription opioid-use disorder has increased for all individuals regardless of their birth cohort membership from the NLAES to the NESARC survey. These findings suggest that more problems (abuse and dependence) may emerge as prescription opioid users get older and that more recent birth cohorts are at higher risk for prescription opioid problems. Martins S, Keyes K, Storr C, Zhu H, Grucza R. Birth-cohort trends in lifetime and past-year prescription opioid-use disorder resulting from nonmedical use: Results from two national surveys. *J Stud Alcohol Drugs*. 2010; 71 (4): 480-487.

Cross-National Differences in Clinically Significant Cannabis Problems: Epidemiologic Evidence from 'Cannabis-Only' Smokers in the United States, Mexico, and Colombia

Epidemiological studies show wide variability in the occurrence of cannabis smoking and related disorders across countries. This study estimated cross-national variation in cannabis users' experience of clinically significant cannabis-related problems in three countries of the Americas, with a focus on cannabis users who may have tried alcohol or tobacco, but who have not used cocaine, heroin, LSD, or other internationally regulated drugs. Data were from the World Mental Health Surveys Initiative and the National Latino and Asian American Study, with probability samples in Mexico (n = 4426), Colombia (n = 5,782) and the United States (n = 8,228). The samples included 212 "cannabis only" users in Mexico, 260 in Colombia and 1,724 in the US. Conditional analysis methods were used to estimate variation in the occurrence of clinically significant problems in cannabis only (CO) users across these surveyed populations. Findings suggested that the experience of cannabis-related problems was infrequent among CO users in these countries, with weighted frequencies ranging from 1% to 5% across survey populations, and with no appreciable cross-national variation in general. CO users in Colombia proved to be an exception. As compared to CO users in the US, the Colombia smokers were more likely to have experienced cannabis-associated "social problems" (odds ratio, OR = 3.0; 95% CI = 1.4, 6.3; p = 0.004) and "legal problems" (OR = 9.7; 95% CI = 2.7, 35.2; p = 0.001). This study suggested similarity in the occurrence of cannabis-related problems in this cross-national comparison within the Americas. Wide cross-national variations in estimated population-level cumulative incidence of cannabis use disorders may be traced to large differences in cannabis smoking prevalence, rather than qualitative differences in cannabis experiences. More research is needed to identify conditions that might make cannabis-related social and legal problems more frequent in Colombia than in the US. Fiestas F, Radovanovic M, Martins S, Medina-Mora M, Posada-Villa J, Anthony J. Cross-national differences in clinically significant cannabis problems: Epidemiologic evidence from 'cannabis-only' smokers in the

United States, Mexico, and Colombia. *BMC Public Health*. 2010; 10 (152): 152-162.

Addiction Treatment and Stable Housing among a Cohort of Injection Drug Users

Unstable housing and homelessness is prevalent among IDU. Researchers sought to examine whether accessing addiction treatment was associated with attaining stable housing in a prospective cohort of IDU in Vancouver, Canada. They used data collected via the Vancouver Injection Drug User Study (VIDUS) between December 2005 and April 2010. Attaining stable housing was defined as two consecutive "stable housing" designations (i.e., living in an apartment or house) during the follow-up period. They assessed exposure to addiction treatment in the interview prior to the attainment of stable housing among participants who were homeless or living in single room occupancy (SRO) hotels at baseline. Bivariate and multivariate associations between the baseline and time-updated characteristics and attaining stable housing were examined using Cox proportional hazard regression models. Of the 992 IDU eligible for this analysis, 495 (49.9%) reported being homeless, 497 (50.1%) resided in SRO hotels, and 380 (38.3%) were enrolled in addiction treatment at the baseline interview. Only 211 (21.3%) attained stable housing during the follow-up period and of this group, 69 (32.7%) had addiction treatment exposure prior to achieving stable housing. Addiction treatment was inversely associated with attaining stable housing in a multivariate model (adjusted hazard ratio [AHR] = 0.71; 95% CI: 0.52-0.96). Being in a partnered relationship was positively associated with the primary outcome (AHR=1.39; 95% CI: 1.02-1.88). Receipt of income assistance (AHR=0.65; 95% CI: 0.44-0.96), daily crack use (AHR=0.69; 95% CI: 0.51-0.93) and daily heroin use (AHR=0.63; 95% CI: 0.43-0.92) were negatively associated with attaining stable housing. In this study, exposure to addiction treatment was negatively associated with attaining stable housing and may have served as a marker of instability in this sample of IDU. Efforts to stably house this vulnerable group may also be underway in contexts separate or outside of addiction treatment. Palepu A, Marshall B, Lai C, Wood E, Kerr T. Addiction treatment and stable housing among a cohort of injection drug users. *PLoS One*. 2010; 5 (7): e11697-e11703.

Factors Associated with Employment among a Cohort of Injection Drug Users

One of the most substantial costs of drug use is lost productivity and social functioning, including holding of a regular job. However, little is known about employment patterns of injection drug users (IDU). This study sought to identify factors associated with legal employment among IDU. Researchers examined the employment patterns of participants in a longitudinal cohort study of IDU in Vancouver, Canada. They used generalized estimating equations (GEE) to determine statistical associations between legal employment and various intrinsic, acquired, behavioral, and circumstantial factors. From June 1999 to November 2003, 330 (27.7%) of 1190 participants reported having a job at some point during follow up. Employment rates remained somewhat stable throughout the study period (9-12.4%). Factors positively and significantly associated with legal employment in multivariate analysis were male gender (adjusted odds ratio [AOR] = 2.78) and living outside the Downtown Eastside (AOR = 1.85). Factors negatively and significantly associated with legal employment included older age (AOR = 0.97); Aboriginal ethnicity (AOR = 0.72); HIV-positive status (AOR = 0.32); HCV-positive status (AOR = 0.46); daily heroin injection (AOR = 0.73); daily crack use (AOR = 0.77); public injecting (AOR = 0.50); sex trade involvement (AOR = 0.49); recent incarceration (AOR = 0.56); and unstable housing (AOR = 0.57). These results suggest a stabilizing effect of employment for IDU and

socio-demographic, drug use and risk-related barriers to employment. There is strong justification to address these barriers and to develop innovative employment programming for high-risk drug users. Richardson L, Wood E, Li K, Kerr T. Factors associated with employment among a cohort of injection drug users. *Drug Alcohol Rev.* 2010; 29 (3): 293-300.

Cannabis Use and Estimated Risk of Later Onset of Depression Spells: Epidemiologic Evidence from the Population-Based World Health Organization World Mental Health Survey Initiative

Early-onset cannabis use is widespread in many countries and might cause later onset of depression, but epidemiologic data across countries are lacking. The authors estimated the suspected causal association that links early-onset (age <17 years) cannabis use with later-onset (age > or =17 years) risk of a depression spell, using data on 85,088 subjects from 17 countries participating in the population-based World Health Organization World Mental Health Survey Initiative (2001-2005). In all surveys, multistage household probability samples were evaluated with a fully structured diagnostic interview for assessment of psychiatric conditions. The association between early-onset cannabis use and later risk of a depression spell was studied using conditional logistic regression with local area matching of cases and controls, controlling for sex, age, tobacco use, and other mental health problems. The overall association was modest (controlled for sex and age, risk ratio = 1.5, 95% confidence interval: 1.4, 1.7), was statistically robust in 5 countries, and showed no sex difference. The association did not change appreciably with statistical adjustment for mental health problems, except for childhood conduct problems, which reduced the association to nonsignificance. This study did not allow differentiation of levels of cannabis use; this issue deserves consideration in future research. de Graaf R, Radovanovic M, van Laar M, Fairman B, Degenhardt L, Aguilar-Gaxiola S, Bruffaerts R, de Girolamo G, Fayyad J, Gureje O, Haro J, Huang Y, Kostychenko S, Lépine J, Matschinger H, Mora M, Neumark Y, Ormel J, Posada-Villa J, Stein D, Tachimori H, Wells J, Anthony J. Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. *Am J Epidemiol.* 2010; 172 (2): 149-159.

No Evidence of Increased Sexual Risk Behavior after Initiating Antiretroviral Therapy among People who Inject Drugs

Although antiretroviral therapy (ART) dramatically reduces viral load and improves survival among HIV-infected injection drug users (IDUs), several short-term studies have raised concerns that ART initiation may result in increases in sexual risk behavior among IDUs. Researchers used data from a long-running cohort of HIV-positive IDUs to examine whether ART initiation was associated with increases in several measures of sexual risk behavior. The date of ART initiation was determined through a validated linkage to a centralized ART dispensation pharmacy. They used generalized linear mixed-effects modeling to determine whether sexual activity, unprotected intercourse, and multiple sexual partnerships were more likely in the 12-month period following ART initiation. Among 457 individuals who were ART naive at baseline, the median age was 34 [interquartile range (IQR) 28-41] and 202 (44.2%) were women. Between May 1996 and April 2008, 260 (56.7%) participants initiated ART. In multivariate analyses, ART initiation was not associated with sexual activity [adjusted odds ratio (AOR) = 0.87, 95% confidence interval (CI) 0.60-1.25], unprotected intercourse (AOR = 0.82, 95% CI 0.51-1.31), or multiple sexual partnerships (AOR = 0.93, 95% CI 0.61-1.40). This study of HIV-positive IDUs failed to detect an increase in sexual risk behavior during the period following ART initiation. Given the known positive effect of ART on survival and its potential role in reducing HIV transmission,

these findings indicate that delivery of ART to IDUs should proceed without concerns that doing so will result in an increase in sexual risk behavior.

Marshall B, Milloy M, Kerr T, Zhang R, Montaner J, Wood E. No evidence of increased sexual risk behavior after initiating antiretroviral therapy among people who inject drugs. *AIDS*. 2010; 24 (14): 2271-2278.

Methadone Use among HIV-positive Injection Drug Users in a Canadian Setting

Researchers examined methadone maintenance therapy (MMT) use among HIV-positive injection drug users (IDU) in Vancouver. Among 353 participants, 199 (56.3%) were on MMT at baseline, and 48 initiated MMT during follow-up. Female gender (adjusted odds ratio [AOR] = 1.73, 95% confidence interval [CI] = 1.14-2.62) and antiretroviral therapy use (AOR = 2.04, 95% CI = 1.46-2.86) were positively associated with MMT use, whereas frequent heroin injection (AOR = 0.34, 95% CI = 0.23-0.50), public injection (AOR = 0.76, 95% CI = 0.59-0.97), syringe borrowing (AOR = 0.54, 95% CI = 0.32-0.90), and nonfatal overdose (AOR = 0.58, 95% CI = 0.36-0.92) were negatively associated with MMT use. The rate of discontinuation of MMT was 12.46 (95% CI = 8.28-18.00) per 100 person years. Frequent heroin use (adjusted hazards ratio = 4.49, 95% CI = 1.81-11.13) was positively associated with subsequent discontinuation of MMT. These findings demonstrate the benefits of MMT among HIV-positive IDU and the need to improve access to and retention in MMT. Pettes T, Wood E, Guillemi S, Lai C, Montaner J, Kerr T. Methadone use among HIV-positive injection drug users in a Canadian setting. *J Subst Abuse Treat*. 2010; 39 (2): 174-179.

Syringe Sharing and HIV Incidence among Injection Drug Users and Increased Access to Sterile Syringes

Researchers assessed the effects of syringe exchange program (SEP) policy on rates of HIV risk behavior and HIV incidence among injection drug users. They used a multivariate generalized estimating equation and Cox regression methods to examine syringe borrowing, syringe lending, and HIV incidence among a prospective cohort of 1228 injection drug users in Vancouver, British Columbia. There were substantial declines in rates of syringe borrowing (from 20.1% in 1998 to 9.2% in 2003) and syringe lending (from 19.1% in 1998 to 6.8% in 2003) following SEP policy change. The declines coincided with a statistically significant increase in the proportion of participants accessing sterile syringes from nontraditional SEP sources ($P < .001$). In multivariate analyses, the period following the change in SEP policy was independently associated with a greater than 40% reduction in syringe borrowing (adjusted odds ratio [AOR] = 0.57; 95% confidence interval [CI] = 0.49, 0.65) and lending (AOR = 0.52; 95% CI = 0.45, 0.60), as well as declining HIV incidence (adjusted hazard ratio = 0.13; 95% CI = 0.06, 0.31). Widespread syringe distribution appears to be a more effective SEP policy than do more restrictive SEP policies that limit syringe access. Efforts should be made to ensure that SEP policies and program design serve to maximize rather than hinder syringe access. Kerr T, Small W, Buchner C, Zhang R, Li K, Montaner J, Wood E. Syringe sharing and HIV incidence among injection drug users and increased access to sterile syringes. *Am J Public Health*. 2010; 100 (8): 1449-1453.

Increased Alcohol Consumption, Nonmedical Prescription Drug Use, and Illicit Drug Use are Associated with Energy Drink Consumption Among College Students

This longitudinal study examined the prevalence and correlates of energy drink use among college students, and investigated its possible prospective associations with subsequent drug use, including nonmedical prescription drug

use. Participants were 1,060 undergraduates from a large, public university who completed three annual interviews, beginning in their first year of college. Use of energy drinks, other caffeinated products, tobacco, alcohol, and other illicit and prescription drugs were assessed, as well as demographic and personality characteristics. Annual weighted prevalence of energy drink use was 22.6% and 36.5% in the second and third year of college, respectively. Compared to energy drink non-users, energy drink users had heavier alcohol consumption patterns, and were more likely to have used other drugs, both concurrently and in the preceding assessment. Regression analyses revealed that Year 2 energy drink use was significantly associated with Year 3 nonmedical use of prescription stimulants and prescription analgesics, but not with other Year 3 drug use, holding constant demographics, prior drug use, and other factors. Findings suggest that a substantial proportion of college students use energy drinks and energy drink users tend to have greater involvement in alcohol and other drug use and higher levels of sensation-seeking, relative to non-users of energy drinks. The authors conclude that more research is needed regarding the health risks associated with energy drink use in young adults, including their possible role in the development of substance use problems. Arria AM, Caldeira KM, Kasperski SJ, O'Grady KE, Vincent KB, Griffiths RR, Wish ED. Increased alcohol consumption, nonmedical prescription drug use, and illicit drug use are associated with energy drink consumption among college students. *J Addict Med.* 2010; 4 (2): 74-80.

Trends in Alcohol-Related Traffic Risk Behaviors Among College Students

Alcohol-impaired driving is a major public health problem. National studies indicate that about 25% of college students have driven while intoxicated in the past month and an even greater percentage drive after drinking any alcohol and/or ride with an intoxicated driver. The purpose of this investigation was to examine the change in these various alcohol-related traffic risk behaviors as students progressed through their college experience. A cohort of 1,253 first-time, first-year students attending a large, mid-Atlantic university were interviewed annually for 4 years. Repeated measures analyses were performed using generalized estimating equations to evaluate age-related changes in prevalence and frequency of each behavior (i.e., ages 19 to 22). Prevalence estimates were statistically weighted to reflect the general population of the first-year students at the university where the sample was recruited. At age 19, 17% of students drove while intoxicated, 42% drove after drinking any alcohol, and 38% rode with an intoxicated driver. For all 3 driving behaviors, prevalence and frequency increased significantly at age 21. Males were more likely to engage in these behaviors than females. To understand the possible relationship of these behaviors to changes in drinking patterns, a post hoc analysis was conducted and revealed that while drinking frequency increased every year, frequency of drunkenness was stable for females, but increased for males. These findings suggest that alcohol-related traffic risk behaviors are quite common among college students and take a significant upturn when students reach the age of 21. The authors conclude that prevention strategies targeted to the college population are needed to prevent serious consequences of these alcohol-related traffic risk behaviors. Beck K, Kasperski S, Caldeira K, Vincent K, O 'Grady K, Arria A. Trends in alcohol-related traffic risk behaviors among college students. *Alcohol Clin Exp Res.* 2010; 34 (8): 1472-1478.

Gender and Age Patterns in HSV-2 and HIV Infection Among Non-Injecting Drug Users in New York City

Researchers examined prevalence of and associations between herpes simplex virus type 2 (HSV-2) infection and HIV infection among never-injecting heroin and cocaine drug users (NIDUs) in New York City. Participants were recruited from patients entering the Beth Israel drug detoxification program. Informed

consent was obtained, a structured questionnaire including demographics, drug use history, and sexual risk behavior was administered, and a blood sample was collected for HIV and HSV-2 antibody testing. A total of 1418 participants who had never (lifetime) injected drugs (NIDUs) were recruited from July 2005 through June 2009. They were primarily male (76%), an average age of 42 years, and Black (67%) or Hispanic (25%). Most reported recent crack cocaine use (74%). Eleven percent of the males reported same sex (MSM) behavior. The prevalence of both viruses was high: for HSV-2, 61% among the total sample, 50% among non-MSM males, 85% among females, and 72% among MSM; for HIV, 16% among the total sample, 12% among non-MSM males, 20% among females, and 46% among MSM. HSV-2 was associated with HIV (OR = 3.2, 95% CI: 2.3-4.5; PR = 2.7, 95% CI: 2.0-3.7). Analyses by gender and age groups indicated different patterns in mono-infection and co-infection for the 2 viruses. These HSV-2 and HIV rates are comparable with rates in sub-Saharan Africa, indicating the urgent need for prevention programs tailored to gender and age group and new platforms for providing services to NIDUs. Des Jarlais D, Arasteh K, McKnight C, Perlman D, Hagan H, Semaan S, Friedman S. Gender and age patterns in HSV-2 and HIV infection among non-injecting drug users in New York City. *Sex Transm Dis.* 2010; 37 (10): 637-643.

Associations Between Conduct Problems and Alcohol Use in Adolescent Girls: The Moderating Role of Race

While a robust relationship has been shown between conduct problems and adolescent alcohol use, the direction of association, particularly in girls, is not well-delineated. This study sought to examine the time-varying developmental associations between conduct problems and early alcohol use in girls between ages 11 and 15 and to test the moderating role of race. The study is based on data collected annually from the oldest cohort in the Pittsburgh Girls Study (n = 566; 56% African American, 44% White). Two models of the association between conduct problems and alcohol use were tested using latent growth curve analyses: conduct-problem-effect (conduct problems predict time-specific variation in alcohol use trajectory) and alcohol-effect (alcohol use predicts time-specific variation in conduct problem trajectory) models. The authors found that girls' conduct problems and alcohol use increased over ages 11-15. Results provided support for a conduct-problem-effect model, although the timing of the associations between conduct problems and alcohol use differed by ethnicity: among White girls, conduct problems prospectively predicted alcohol use at ages 11-13 but not later, whereas among African American girls, prospective prediction was observed at ages 13-14 but not earlier. The authors conclude that there are developmental differences in the time-varying association of conduct problems and alcohol use during early adolescence for African American and White girls. Ethnic differences in the development of alcohol use warrant further study, and have potential implications for culture-specific early screening and preventive interventions. Loeber R, Stepp S, Chung T, Hipwell A, White H. Time-varying associations between conduct problems and alcohol use in adolescent girls: the moderating role of race. *J Stud Alcohol Drugs.* 2010; 71 (4): 544-553.

Comparing Respondent-Driven Sampling and Targeted Sampling Methods of Recruiting Injection Drug Users in San Francisco

Researchers compared demographic characteristics, risk behaviors, and service utilization among injection drug users (IDUs) recruited from two separate studies in San Francisco in 2005, one which used targeted sampling (TS) and the other which used respondent-driven sampling (RDS). IDUs were recruited using TS (n = 651) and RDS (n = 534) and participated in quantitative interviews that included demographic characteristics, risk behaviors, and service utilization. Prevalence estimates and 95% confidence intervals (CIs) were calculated to assess whether there were differences in these variables by

sampling method. There was overlap in 95% CIs for all demographic variables except African American race (TS: 45%, 53%; RDS: 29%, 44%). Maps showed that the proportion of IDUs distributed across zip codes were similar for the TS and RDS sample, with the exception of a single zip code that was more represented in the TS sample. This zip code includes an isolated, predominantly African American neighborhood where only the TS study had a field site. Risk behavior estimates were similar for both TS and RDS samples, although self-reported hepatitis C infection was lower in the RDS sample. In terms of service utilization, more IDUs in the RDS sample reported no recent use of drug treatment and syringe exchange program services. This study suggests that perhaps a hybrid sampling plan is best suited for recruiting IDUs in San Francisco, whereby the more intensive ethnographic and secondary analysis components of TS would aid in the planning of seed placement and field locations for RDS. Kral A, Malekinejad M, Vaudrey J, Martinez A, Lorvick J, McFarland W, Raymond H. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. *J Urban Health*. 2010; 87 (5): 839-850.

Access to Sterile Syringes through San Francisco Pharmacies and the Association with HIV Risk Behavior among Injection Drug Users

Increased options for syringe acquisition and disposal have been associated with reductions in high-risk behaviors. This study determined the extent of pharmacy uptake in accessing syringes among injection drug users (IDUs) and estimated associations between pharmacy uptake and safer injection/disposal practices. Two years after the implementation of California's Disease Prevention Demonstration Project, which removed restrictions to non-prescription syringe sales through pharmacies with local authorization, IDUs were recruited through street outreach in San Francisco and interviewed regarding recent syringe acquisition, use, and disposal. The sample of 105 persons included a high proportion of men (67%), people of color (49%), and homeless persons (71%). The most common syringe source was a syringe exchange program (SEP) (80%), with pharmacies being accessed by 39% of respondents. The most commonly cited source of disposal was a SEP (65%), with very few reports of pharmacy disposal (2%). Adjusted analysis showed that unsuccessful attempts to purchase syringes at a pharmacy increased the odds of both injecting with a used syringe and giving away a used syringe. Using a SEP decreased the odds of unsafe injection and disposal practices. Thus, 2 years after the initiation of the California Disease Prevention Demonstration Project, results from this small study suggest that SEPs still provide the majority of syringe distribution and disposal services to San Francisco IDUs; however, pharmacies now augment syringe access. In addition, unsafe injection behavior is reported more often among those who do not use these syringe sources. These results are consistent with prior studies in suggesting that increasing the availability of syringes through SEPs and pharmacies, and developing bridges between them, may further reduce syringe-related risk. Riley E, Kral A, Stopka T, Garfein R, Reuckhaus P, Bluthenthal R. Access to sterile syringes through San Francisco pharmacies and the association with HIV risk behavior among injection drug users. *J Urban Health*. 2010; 87 (4): 534-542.

Prevalence, Correlates, and Viral Dynamics of Hepatitis Delta among Injection Drug Users

Most hepatitis delta virus (HDV) prevalence estimates from the United States are >10 years old, and HDV has shown significant temporal variation in other populations. HDV-hepatitis B virus (HBV) dual infection progresses rapidly, has more complications, and has a different treatment regimen than HBV infection alone. Accurate estimates of prevalence and risk factors are important to help

clinicians decide who to screen. Injection drug users in Baltimore, Maryland, who were positive for HBV serologic markers were tested for hepatitis delta antibody (HDAb) at 2 time periods: 1988-1989 (194 participants) and 2005-2006 (258 participants). Those who were HDAb positive in 2005-2006, plus a random sample of HDAb negative, HBV-positive participants were tested for HDV RNA, HBV DNA, and HCV RNA. Characteristics associated with HDV exposure and viremia were identified. HDV prevalence declined from 15% in 1988-1989 to 11% in 2005-2006. Among those with chronic HBV infection, prevalence increased from 29% (14 of 48 participants) to 50% (19 of 38 participants) ($P=.05$). Visiting a "shooting gallery" (a location where people gather to inject illegal drugs) was a strong correlate of HDAb positivity (relative risk, 3.08; $P=.01$). Eight (32%) of those who were HDAb positive had HDV viremia. Viremic participants had elevated liver enzyme levels and more emergency room visits. These findings on the temporal increase in HDV prevalence among persons with chronic HBV infection are troubling. More careful study is needed to understand this change and to identify prevention priorities to keep the burden from increasing. Kucirka L, Farzadegan H, Feld J, Mehta S, Winters M, Glenn J, Kirk G, Segev D, Nelson K, Marks M, Heller T, Golub E. Prevalence, correlates, and viral dynamics of Hepatitis Delta among injection drug users. *J Infect Dis.* 2010; 202 (6): 845-852.

Assessing Correlates of the Growth and Extent of Methamphetamine Abuse and Dependence in California

Using aggregate-level data, this study performed cross-sectional analyses on all 1,628 populated California zip code areas and longitudinal analyses on 581 consistently defined zip codes over six years (1995-2000), relating place and population characteristics of these areas to rates of hospital discharges for amphetamine dependence/abuse using linear spatial models. Analyzing the data in two ways, spatial time series cross-sections and spatial difference models, amphetamine dependence/abuse were greatest in rural areas with more young low-income whites, larger numbers of retail and alcohol outlets, and smaller numbers of restaurants. Growth rates of these problems were greater in areas with higher income and larger non-White and Hispanic populations. This suggests that there was some change in the penetration of the methamphetamine epidemic into different population groups during this time. Study implications and limitations are discussed. Gruenewald P, Johnson F, Ponicki W, Remer L, Lascala E. Assessing correlates of the growth and extent of methamphetamine abuse and dependence in California. *Subst Use Misuse.* 2010; 45 (12): 1948-1970.

Determinants of Hospitalization for a Cutaneous Injection-Related Infection among Injection Drug Users: a Cohort Study

Cutaneous injection-related infections (CIRI) are a primary reason individuals who inject drugs (IDU) are hospitalized. The objective of this study was to investigate determinants of hospitalization for a CIRI or related infectious complication among a cohort of supervised injection facility (SIF) users. From January 1, 2004 to January 31, 2008, researchers examined determinants of hospitalization for a CIRI or related infectious complication, based on ICD 10 codes, among 1083 IDU recruited from within the SIF. Length of stay in hospital and cost estimates, based on a fully-allocated costing model, was also evaluated. Among hospital admissions, 49% were due to a CIRI or related infectious complication. The incidence density for hospitalization for a CIRI or related infectious complication was 6.07 per 100 person-years (95% confidence intervals [CI]: 4.96 - 7.36). In the adjusted Cox proportional hazard model, being HIV positive (adjusted hazard ratio [AHR] = 1.79 [95% CI: 1.17 - 2.76]) and being referred to the hospital by a nurse at the SIF (AHR = 5.49 [95% CI: 3.48 - 8.67]) were associated with increased hospitalization. Length of stay in hospital was significantly shorter among participants referred to the hospital by

a nurse at the SIF when compared to those who were not referred (4 days [interquartile range {IQR}: 2-7] versus 12 days [IQR: 5-33]) even after adjustment for confounders ($p = 0.001$). This study found that a strong predictor of hospitalization for a CIRI or related infectious complication was being referred to the hospital by a nurse from the SIF, indicating that nurses not only facilitate hospital utilization but may provide early intervention that can prevent lengthy and expensive hospital visits for a CIRI or related infectious complication. Lloyd-Smith E, Wood E, Zhang R, Tyndall M, Sheps S, Montaner J, Kerr T. Determinants of hospitalization for a cutaneous injection-related infection among injection drug users: A cohort study. *BMC Public Health*. 2010; 10: 327-334.

Correlates of Heterosexual Anal Intercourse among Substance-Using Club-Goers

Anal sexual intercourse is a risk factor for transmission of HIV, yet much of what is known about anal sex is based on men who have sex with men (MSM). Much less is known about anal sex among heterosexuals, especially among those who also use illicit substances. The present study examined the demographic, sexual behaviors, substance use, and psychosocial correlates of recent anal intercourse among heterosexual young adult nightclub goers. Data were drawn from an on-going natural history study of participants ($n = 597$) in Miami's club scene who use club drugs and prescription medications for non-medical reasons, and who regularly attend nightclubs. Participants who reported anal sex ($n = 118$) were more likely to be male, of moderate income, Latino, trade sex, have unprotected sex, and report victimization. These findings suggest that interventions that target heterosexual populations should include discussions of the risks of anal intercourse. Event-based and qualitative studies will be important to better understand the context in which anal sex heterosexual substance users occurs. Ibañez G, Kurtz S, Surratt H, Inciardi J. Correlates of heterosexual anal intercourse among substance-using club-goers. *Arch Sex Behav*. 2010; 39(4): 959-967.

Determinants of Alcohol Consumption in HIV-Uninfected Injection Drug Users

Researchers assessed the association between time fixed and time varying participant characteristics and subsequent alcohol consumption in 1,968 IDUs (median age 37 years, 28% female, 90% African-American) followed semi-annually from 1988 to 2008. The median alcohol consumption was seven drinks per week at study entry (first and third quartile: 1, 26) with 36% reporting binge drinking (consuming more than 5 drinks at any one occasion). Alcohol consumption and binge drinking decreased over the follow-up period. Older individuals and women reported consuming fewer drinks per week. More typical alcohol consumption was reported by those who also reported non-injection cocaine use, injection drug use, having one or more sex partners, or among men, a same sex partner, in the past 6 months. These associations were similar for drinks per week and for binge drinking. This study demonstrates that, in a large urban cohort with a history of injection drug use, risky drug use and sexual risk behavior are associated with subsequent alcohol consumption. Sander P, Cole S, Ostrow D, Mehta S, Kirk G. Determinants of alcohol consumption in HIV-uninfected injection drug users. *Drug Alcohol Depend*. 2010; 111(1-2): 173-176.

Modeling Crack Cocaine Use Trends over 10 Years in a Canadian Setting

Crack cocaine use among illicit drug users is associated with a range of health and community harms. However, long-term epidemiological data documenting

patterns and risk factors for crack use initiation remain limited, especially among IDUs. Researchers investigated longitudinal patterns of crack cocaine use among injection drug users enrolled in a prospective cohort study in Vancouver, Canada between 1996 and 2005. They used a Cox proportional hazards regression analysis to identify independent predictors of crack use initiation among the cohort. In total, 1603 IDUs were recruited between May 1996 and December 2005. At baseline, 7.4% of participants reported ever using crack. This increased to 42.6% by the end of the study period (Mantel trend test $P < 0.001$). Independent predictors of crack use initiation during the study period included frequent cocaine injection, crystal methamphetamine injection, residing in the city's drug using epicenter, and involvement in the sex trade (all $P < 0.05$). These findings demonstrate a massive increase in crack use among IDUs over the 9 year period and highlight the complex interactions that contribute to the initiation of crack use among IDUs. Evidence-based interventions are urgently needed to address crack use initiation and the harms associated with its ongoing use. Werb D, Debeck K, Kerr T, Li K, Montaner J, Wood E. Modeling crack cocaine use trends over 10 years in a Canadian setting. *Drug Alcohol Rev.* 2010; 29 (3): 271-277.

Hunger and Associated Harms among Injection Drug Users in an Urban Canadian Setting

Food insufficiency is often associated with health risks and adverse outcomes among marginalized populations. However, little is known about correlates of food insufficiency among injection drug users (IDU). Researchers conducted a cross-sectional study to examine the prevalence and correlates of self-reported hunger in a large cohort of IDU in Vancouver, Canada. Food insufficiency was defined as reporting "I am hungry, but don't eat because I can't afford enough food." Logistic regression was used to determine independent socio-demographic and drug-use characteristics associated with food insufficiency. Among 1,053 participants, 681 (64.7%) reported being hungry and unable to afford enough food. Self-reported hunger was independently associated with: unstable housing (adjusted odds ratio [AOR]: 1.68, 95% confidence interval [CI]: 1.20 - 2.36, spending about \$50/day on drugs (AOR: 1.43, 95% CI: 1.06 - 1.91), and symptoms of depression (AOR: 3.32, 95% CI: 2.45 - 4.48). These findings suggest that IDU in this setting would likely benefit from interventions that work to improve access to food and social support services, including addiction treatment programs which may reduce the adverse effect of ongoing drug use on hunger. Anema A, Wood E, Weiser S, Qi J, Montaner J, Kerr T. Hunger and associated harms among injection drug users in an urban Canadian setting. *Subst Abuse Treat Prev Policy.* 2010; 5: 20-27.

Are Young Injection Drug Users Ready and Willing to Participate in Preventive HCV Vaccine Trials?

Trials to evaluate the efficacy of preventive HCV vaccines will need participation from high risk HCV seronegative IDUs. To guide trial planning, researchers assessed willingness of young IDU in San Francisco to participate in HCV vaccine efficacy trials and evaluate knowledge of vaccine trial concepts: placebo, randomization, and blinding. During 2006 and 2007, a total of 67 participants completed the survey. A substantial proportion (88%) would definitely (44%) or probably (44%) be willing to participate in a randomized trial, but knowledge of vaccine trial concepts was low. Reported willingness to participate in an HCV vaccine trial decreased with increasing trial duration, with 67% of participants surveyed willing to participate in a trial of 1 year duration compared to 43% of participants willing to participate in a trial of 4 years duration. Willingness to enroll in HCV vaccine trials was higher in young IDU than reported by most at-risk populations in HIV vaccine trials. Educational strategies will be needed to ensure understanding of key concepts prior to implementing HCV vaccine trials. Levy V, Evans J, Stein E, Davidson P, Lum P,

Hahn J, Page K. Are young injection drug users ready and willing to participate in preventive HCV vaccine trials? *Vaccine*. 2010; 28(37): 5947-5951.

Hepatitis C Virus Risk Behaviors within the Partnerships of Young Injecting Drug Users

Young IDUs are at high risk for hepatitis C virus (HCV). Researchers sought to determine whether perceiving one's injecting partner to be HCV positive was associated with decreased odds of engaging in receptive needle/syringe sharing (RNS) or ancillary equipment sharing (AES) with that partner. They conducted a cross sectional study from 2003 to 2007 in San Francisco with 212 young (under age 30) IDU who were HCV antibody negative and who reported on 492 injecting partner-ships. The measures used were self-reported RNS and AES within injecting partnerships. RNS and AES (in the absence of RNS) occurred in 23% and 64% of injecting partnerships in the prior month. The odds of engaging in RNS were significantly lower for relationships in which the participant reported that his/her partner was HCV positive (odds ratio [OR] 0.49; 95% confidence interval [CI] 0.25-0.95). This association was attenuated when adjusted for reusing one's own needle/syringe (adjusted OR 0.57; 95% CI 0.28-1.15). The odds of engaging in AES were lower for participants who did not know the HCV status of their partner and only among non-sexual partnerships (OR 0.47; 95% CI 0.29-0.76). Given that perceiving one's partner to be HCV positive was associated with decreased RNS, increased HCV testing and partner disclosure is warranted. AES was common and found to be less among only non-sexual partnerships in which the HCV status of the partner was not known. The variety of injecting partnerships among young IDU suggests that interventions to reduce AES within this population must be widespread. Hahn J, Evans J, Davidson P, Lum P, Page K. Hepatitis C virus risk behaviors within the partnerships of young injecting drug users. *Addiction*. 2010; 105(7): 1254-1264.

The Challenge of Pregnancy among Homeless Youth: Reclaiming a Lost Opportunity

Young, homeless women often become pregnant, but little is known about how street youth experience their pregnancies. Researchers documented 26 pregnancy outcomes among 13 homeless women (ages 18-26) and eight homeless men through interviews and participant-observation. Eight pregnancies were voluntarily terminated, three were miscarried, and fifteen were carried to term. Regardless of pregnancy outcome, street youths' narratives focused on ambivalence about parenting, traumatic childhood experiences, and current challenges. Despite significant obstacles, almost all were convinced of their personal capacity to change their lives. While most wanted to be parents, the majority lost custody of their newborns and consequently associated contact with medical and social services with punitive outcomes. Most of the youth who chose to terminate successfully sought safe medical care. Recommendations are offered for changing the approach of services to take full advantage of pregnancy as a potential catalyst event for change in this highly vulnerable and underserved population. Smid M, Bourgois P, Auerswald C. The challenge of pregnancy among homeless youth: reclaiming a lost opportunity. *J Health Care Poor Underserved*. 2010; 21 (2 Suppl): 140-156.

Who Chooses a Rapid Test for HIV in Los Angeles County, California?

The purpose of this study was to determine who chooses a rapid test for HIV when given a choice in a community-based or mobile van setting in Long Beach, California. Individuals were given a choice of either rapid or standard

HIV testing either alone or in conjunction with testing for sexually transmitted diseases (STD). Of the 2,752 HIV tests performed between March 2005 and March 2009, 917 (33%) were rapid tests. Preference for rapid HIV testing was among men who have sex with men (MSM), who reported using alcohol in the last 48 hours but who did not report the use of illicit drugs. Individuals reporting sex trading were also more likely to choose the rapid HIV test. African Americans, regardless of sexual identification, were significantly less likely to choose the HIV rapid test. These findings indicate that strategies are needed to encourage HIV rapid testing among both noninjection and injection drug users and other at-risk groups. Marsh K, Reynolds G, Rogala B, Fisher D, Napper L. Who chooses a rapid test for HIV in Los Angeles County, California? *Eval Health Prof.* 2010; 33(2): 177-196.

The Longitudinal Consistency of Mother-Child Reporting Discrepancies of Parental Monitoring and Their Ability to Predict Child Delinquent Behaviors Two Years Later

This study examined the longitudinal consistency of mother-child reporting discrepancies of parental monitoring and whether these discrepancies predict children's delinquent behaviors two years later. Participants included 335 mother/female-caregiver and child (46% boys, >90% African American; age range 9-16 years [M = 12.11, SD = 1.60]) dyads living in moderate-to-high violence areas. Mother-child discrepancies were internally consistent within multiple assessment points and across measures through a 2-year follow-up assessment. Further, mothers who at baseline consistently reported higher levels of parental monitoring relative to their child had children who reported greater levels of delinquent behaviors two years later, relative to mother-child dyads that did not evidence consistent discrepancies. This finding could not be accounted for by baseline levels of the child's delinquency, maternal and child emotional distress, or child demographic characteristics, nor was it replicated when relying on the individual reports of parental monitoring to predict child delinquency. This suggests that mother-child reporting discrepancies provided information distinct from the absolute frequency of reports. Such discrepancies may have potential as new individual differences measurements in developmental psychopathology research. De Los Reyes A, Goodman K, Kliewer W, Reid-Quiñones K. The longitudinal consistency of mother-child reporting discrepancies of parental monitoring and their ability to predict child delinquent behaviors two years later. *J Youth Adolesc.* 2010; 39 (12): 1417-1430.

Drug-Related Risks among Street Youth in Two Neighborhoods in a Canadian Setting

Researchers compared drug-related behaviors, including initiation of drug use, among street youth residing in two adjacent neighborhoods in Vancouver. One neighborhood, the Downtown Eastside (DTES), features a large open-air illicit drug market. In multivariate analysis, having a primary illicit income source (adjusted odds ratio [AOR] = 2.64, 95% confidence interval [CI]: 1.16-6.02) and recent injection heroin use (AOR = 4.25, 95% CI: 1.26-14.29) were positively associated with DTES residence, while recent non-injection crystal methamphetamine use (AOR: 0.39, 95% CI: 0.16-0.94) was negatively associated with DTES residence. In univariate analysis, dealing drugs (odds ratio [OR] = 5.43, 95% CI: 1.24-23.82) was positively associated with initiating methamphetamine use in the DTS compared to the DTES. These results demonstrate the importance of considering neighborhood variation when developing interventions aimed at reducing drug-related harms among street-involved youth at various levels of street entrenchment. Werb D, Kerr T, Fast D, Qi J, Montaner J, Wood E. Drug-related risks among street youth in two neighborhoods in a Canadian setting. *Health Place.* 2010; 16(5): 1061-1067.

Harmful Microinjecting Practices among a Cohort of Injection Drug Users in Vancouver Canada

Researchers sought to identify factors associated with harmful microinjecting practices in a longitudinal cohort of IDU. Using data from the Vancouver Injection Drug Users Study (VIDUS) between January 2004 and December 2005, generalized estimating equations (GEE) logistic regression was performed to examine sociodemographic and behavioral factors associated with four harmful microinjecting practices (frequent rushed injecting, frequent syringe borrowing, frequently injecting with a used water capsule, frequently injecting alone). In total, 620 participants were included in the analysis, of which 251 (40.5%) were women and 203 (32.7%) self-identified as Aboriginal. The median age was 31.9 (interquartile range: 23.4-39.3). GEE analyses found that each harmful microinjecting practice was associated with a unique profile of sociodemographic and behavioral factors. High rates of harmful microinjecting practices were observed among these IDU. The emerging epidemiology of harmful microinjecting practices points to the need for strategies that target higher risk individuals, including the use of peer-driven programs and drug-specific approaches, in an effort to promote safer injecting practices and reduce the spread of bloodborne diseases. Rachlis B, Lloyd-Smith E, Small W, Tobin D, Stone D, Li K, Wood E, Kerr T. Harmful microinjecting practices among a cohort of injection drug users in Vancouver Canada. *Subst Use Misuse*. 2010; 45(9): 1351-1366.

Physical Punishment as a Specific Childhood Adversity Linked to Adult Drinking Consequences: Evidence from China

This study estimated the association between childhood physical punishment (CPP) and level of alcohol use disorder (AUD), using two different approaches to take other childhood adversities into account. Findings were based upon data from a population survey using face-to-face interviews with a representative sample of non-institutionalized adult residents of Beijing and Shanghai, China. A total of 5201 participants aged 18-70 years were interviewed using a version of the World Mental Health Composite International Diagnostic Interview. Standardized assessments covered early life experiences of childhood physical punishment, other childhood adversities, parental drinking problems, childhood conduct problems and clinical features of AUD. A strong association was found linking CPP and level of AUD, with other childhood adversities held constant (probit coefficient=0.70, 95% CI=0.40, 1.00) via covariate terms in structural equations modeling. Furthermore, there was evidence that CPP might exert an additional influence on level of AUD over and above a generally noxious family environment (probit coefficient=0.20, 95% CI=0.02, 0.38). The researchers conclude that there appears to be a robust association between reports of harsh punishment in childhood and alcohol dependence in adulthood adjusting for a range of possible confounding factors. Whether the association is causal or whether both are related to a common underlying factor or recall bias needs to be investigated further. Cheng HG, Anthony JC, Huang Y. Harsh physical punishment as a specific childhood adversity linked to adult drinking consequences: Evidence from China. *Addiction*. 2010; 105(8): 1323-1330.

The Effects of Unequal Access to Health Insurance for Same-Sex Couples in California

Inequities in marriage laws and domestic partnership benefits may have implications for those who bear the burden of health care costs. Researchers examined recent data from the California Health Benefits Survey, a representative survey of >100,000 California residents, to illuminate disparities in health insurance coverage faced by same-sex couples. Partnered gay men

were less than half as likely (42 percent) as married heterosexual men to get employer-sponsored dependent coverage, and partnered lesbians have an even slimmer chance (28 percent) of getting dependent coverage compared to married heterosexual women. As a result of these much lower rates of employer-provided coverage, partnered lesbians and gay men are more than twice as likely to be uninsured as married heterosexuals. The researchers suggest that the exclusion of gay men and women from civil marriage and the failure of domestic partnership benefits to provide insurance parity contribute to unequal access to health coverage, with the probable result that more health spending is pushed onto these individuals and onto the public. Ponce N, Cochran S, Pizer J, Mays V. The effects of unequal access to health insurance for same-sex couples in California. *Health Aff (Millwood)*. 2010; 29 (8): 1539-1548.

The Mediating Effect of Childhood Abuse in Sexual Orientation Disparities in Tobacco and Alcohol Use during Adolescence: Results from the Nurses' Health Study II

Researchers examined the mediating effect of childhood abuse on sexual orientation disparities in tobacco and alcohol use during adolescence. They analyzed data from over 62,000 women in the ongoing Nurses' Health Study II cohort who provided information on sexual orientation, childhood abuse occurring by age 11, and tobacco and alcohol use in adolescence. They used multivariate regression analyses, controlling for confounders, to estimate the mediating effect of childhood abuse on the association between sexual orientation and tobacco and alcohol use in adolescence. Lesbian and bisexual orientation and childhood abuse were positively associated with greater risk of tobacco and alcohol use during adolescence. For lesbians, the estimated proportion of excess tobacco and alcohol use in adolescence relative to use among heterosexual women that was mediated by abuse in childhood ranged from 7 to 18%; for bisexual women, the estimated proportion of excess use mediated by abuse ranged from 6 to 13%. Elevated childhood abuse in lesbian and bisexual women partially mediated excess tobacco and alcohol use in adolescence relative to heterosexual women. Interventions to prevent child abuse may reduce sexual orientation disparities in some of the leading causes of cancer in women. Jun H, Austin S, Wylie S, Corliss H, Jackson B, Spiegelman D, Pazaris M, Wright R. The mediating effect of childhood abuse in sexual orientation disparities in tobacco and alcohol use during adolescence: Results from the Nurses' Health Study II. *Cancer Causes Control*. 2010; 21 (11): 1817-1828.

Intimate Partner Violence and Consistent Condom Use among Drug-Using Heterosexual Women in New York City

This study examined the associations of relationship factors, partner violence, relationship power, and condom-use related factors with condom use with a main male partner among drug-using women. Over two visits, 244 heterosexual drug-using women completed a cross-sectional survey. Multivariate logistic regression models indicated that women who expected positive outcomes and perceived lower condom-use barriers were more likely to report condom use with their intimate partners. The findings suggest that future interventions aiming at reducing HIV risk among drug-using women should focus on women's subjective appraisals of risks based on key relationship factors in addition to the occurrence of partner violence. Panchanadeswaran S, Frye V, Nandi V, Galea S, Vlahov D, Ompad D. Intimate partner violence and consistent condom use among drug-using heterosexual women In New York City. *Women Health*. 2010; 50(2): 107-124.

Psychiatric Morbidity, Violent Crime, and Suicide among Children

and Adolescents Exposed to Parental Death

This retrospective cohort study examined the risk for suicide, psychiatric hospitalization, and violent criminal convictions among offspring of parents who died from suicide, accidents, and other causes. Population-based data from multiple Swedish national registers were linked from 1969 to 2004. Participants were 44,397 offspring of suicide decedents, 41,467 offspring of accident decedents, 417,365 offspring of parents who died by other causes, and 3,807,867 offspring of alive parents. The researchers estimated risk by mode of parental death (suicide, accident, other) and offspring age at parental death (childhood, adolescence, young adulthood). Offspring of suicide decedents were at greater risk for suicide than offspring of alive parents (incidence rate ratio [IRR] = 1.9; 95% confidence interval [CI] = 1.4 to 2.5), whereas offspring of accident decedents and other parental death were not at increased risk ($p < .001$). The risk for offspring suicide differed by the developmental period during which parental suicide occurred. Child and adolescent offspring of suicide decedents were at threefold greater risk for suicide (IRR = 3.0; 95% CI = 1.7 to 5.3; IRR = 3.1, 95% CI = 2.1 to 4.6, respectively). Young adults were not at increased risk for suicide (IRR = 1.3; 95% CI = 0.9 to 1.9). Offspring of suicide decedents had an especially high risk of hospitalization for suicide attempt, depressive, psychotic, and personality disorders. Child survivors of parental suicide were at particularly high risk for hospitalization for drug disorders and psychosis. All offspring who experienced parental death, regardless of mode or age, were at increased risk for violent criminal convictions. The findings support that mode of parental death and offspring age at parental death are associated with offspring long-term risk for suicide and hospitalization for specific psychiatric disorders. Wilcox H, Kuramoto S, Lichtenstein P, LEngström N, Brent D, Runeson B. Psychiatric morbidity, violent crime, and suicide among children and adolescents exposed to parental death. *J Am Acad Child Adolesc Psychiatry*. 2010; 49 (5): 514-523.

Differential Racial/Ethnic Patterns in Substance Use Initiation Among Young, Low-Income Women

Substance abuse has been associated with a host of health problems, as well as impaired social, relationship, and vocational functioning. The current study examines racial and ethnic differences in patterns of initiation of licit and illicit substance use among low-income women. A cross-sectional survey was conducted among 696 low-income women between the ages of 18 and 31 who sought gynecological care between December, 2001 and May, 2003 in southeast Texas. Overall, White women fit the classic profile of drug use initiation patterns, with those initiating tobacco and beer/wine at earlier ages being more likely to use illicit drugs. Conversely, African-American and Hispanic women initiated tobacco and beer/wine at much later ages than White women, but they were as likely to use illicit drugs. This study extends the literature by examining patterns of drug initiation among a critically underserved sample of low-income, ethnically-diverse women. Initiation of licit substance use at earlier ages was generally a risk factor for later illicit use. These findings further emphasize the importance of implementing substance use prevention programs at an early age, and focusing on the elevated risk of early initiation on later substance use disorders. Wu Z, Temple J, Shokar N, Nguyen-Oghalai T, Grady J. Differential racial/ethnic patterns in substance use initiation among young, low-income women. *Am J Drug Alcohol Abuse*. 2010; 36 (2): 123-129.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Prevention Research

Web-Based Selective Prevention of Marijuana Use for College Students

The current study was designed to evaluate a brief, web-based personalized feedback intervention for at-risk marijuana users transitioning to college. All entering first-year students were invited to complete a brief questionnaire. Participants were eligible to participate if they used marijuana in the 3 months prior to screening. Participants completed a baseline assessment (N = 341) and were randomly assigned to web-based personalized feedback or an assessment-only control condition. Participants completed 3-month (95.0%) and 6-month (94.4%) follow-up assessments. Results indicated that although there was no overall intervention effect, moderator analyses found promising effects for those with a family history of drug problems and, to a smaller extent, students who were higher in contemplation of changing marijuana use at baseline. Although prior research regarding development of motivational feedback interventions for college alcohol and drug use has been promising, the web-based mode of delivery of this feedback was quite different than in the majority of prior studies, suggesting that interventions that do not actively include in-person motivational interviewing strategies, and instead rely solely on feedback reports, may not work well with marijuana-involved emerging adults. Additional implications of these findings selective interventions for college marijuana use and web-based interventions in general are discussed. Lee C, Neighbors C, Kilmer J, Larimer M. A brief, web-based personalized feedback selective intervention for college student marijuana use: A randomized clinical trial. *Psychol Addict Behav.* 2010; 24 (2): 265-273.

Models for Large-Scale Implementation of Drug Abuse Prevention Interventions Increases Adoption and Utilization of Evidence-Based Approaches

Although advances in prevention science over the past two decades have produced a growing list of tested and effective programs and policies for preventing adolescent delinquency and drug use, widespread dissemination and high-quality implementation of effective programs and policies in communities has not been achieved. The Community Youth Development Study (CYDS) is a randomized, community-level trial of the Communities That Care (CTC) system for promoting science-based prevention in communities. This study compared 12 community prevention coalitions implementing the CTC system in 12 intervention communities as part of the CYDS to prevention coalitions located in the 12 control communities. As hypothesized, the CYDS coalitions implemented significantly more of the CTC core intervention elements (e.g., using community-level data on risk and protective factors to guide selection of effective prevention programs), and also implemented

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significantly greater numbers of tested, effective prevention programs than the prevention coalitions in the control communities. Implications of the findings for efforts to achieve widespread dissemination of effective prevention programs, policies, and practices are discussed. Arthur MW, Hawkins JD, Brown EC, Briney JS, Oesterle S. Implementation of the communities that care prevention system by coalitions in the community youth development study. *J Community Psychol.* 2010; 38 (2): 245-258.

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Anti-tobacco Industry PSAs More Effective when Message Delivered Explicitly Rather than Implicitly

Televised anti-smoking public service announcements (PSAs) are a part of successful smoking prevention campaigns aimed at adolescents. Anti-smoking PSAs employ several different anti-smoking messages, for example, the tobacco industry is deceptive; smoking is addictive; and smoking has long term health effects. However, there is little agreement about which messages are most effective at changing adolescents' smoking behavior. Moreover, the method used to deliver tobacco industry manipulation messages in anti-smoking PSAs has not yet been examined, but may be related to their efficacy. In particular, the extent to which anti-smoking messages are delivered implicitly (i.e., indirectly) or explicitly (i.e., directly) has not been addressed. Specifically, message content in anti-smoking public service announcements (PSAs) can be delivered explicitly (directly with concrete statements) or implicitly (indirectly via metaphor), and the method of delivery may affect the efficacy of those PSAs. The purpose of this study was to conduct an initial test of this idea using tobacco industry manipulation PSAs in adolescents. A 2 (age: 11-14 years old; 15-17 years old) x2 (message delivery: implicit, explicit) mixed model study design was used. The sample (n=110) was 55% female with diverse ethnic representation (38% Caucasian; 53% African-American; 2% Asian; 2% Native American; and 5% multi-ethnic); their mean age was 14.1 (SD=1.8). A total of n=22 (18%) reported smoking at least a puff of a cigarette in the past; none were current smokers. Analyses revealed a significant main effect of message delivery: Tobacco industry manipulation PSAs that delivered their messages explicitly were associated with stronger levels of smoking resistance self-efficacy compared to tobacco industry manipulation PSAs that delivered their messages implicitly. No significant main effects of age were found nor were any interactions between age and message delivery. These results suggest that message delivery factors should be taken into account when designing anti-smoking PSAs. Shadel W, Fryer C, Tharp-Taylor S. Tobacco industry manipulation messages in anti-smoking public service announcements: The effect of explicitly versus implicitly delivering messages. *Addict Behav.* 2010; 35 (5): 526-529.

Pilot Attachment-Based Intervention for Mothers in Substance Abuse Treatment Improves Parenting

This study reports post-treatment findings from a randomized pilot study testing the preliminary efficacy of the Mothers and Toddlers Program (MTP), a 12 week attachment-based individual parenting therapy for mothers enrolled in substance abuse treatment and caring for children ages birth to 36 months. Forty-seven mothers were randomized to MTP versus the Parent Education Program (PE), a comparison intervention providing individual case management and child guidance brochures. At post-treatment, MTP mothers demonstrated better reflective functioning (capacity to recognize intentions and emotional needs of child) in the Parent Development Interview, representational coherence and sensitivity (quality of representations of the child), and care-giving behavior than PE mothers. Partial support was also found for proposed mechanisms of change in the MTP model. Together, preliminary findings suggest that attachment-based interventions may be more

effective than traditional parent training for enhancing relationships between substance using women and their young children. Suchman N, DeCoste C, Castiglioni N, McMahon T, Rounsaville B, Mayes L. The mothers and toddlers program, an attachment-based parenting intervention for substance using women: Post-treatment results from a randomized clinical pilot. *Attach Hum Dev.* 2010; 12 (5): 483-504.

Pilot Trial of a Couple-based HIV/STI Risk Reduction Study in Kazakhstan

This pilot randomized controlled trial in Kazakhstan aimed to adapt and test the feasibility of a couple-based HIV/STI risk-reduction intervention (CHSR) for couples who are injecting drug users (IDUs). The study examined the preliminary effects of the intervention versus an attentional control wellness promotion (WP) condition on HIV risk behavioral outcomes among 40 couples who are IDUs (n = 80 participants). Compared with WP participants, CHSR participants were significantly more likely to increase condom use and decrease unsafe injection acts at the 3-month follow-up. This pilot trial demonstrates the feasibility and preliminary effects of the CHSR in reducing drug-related and sexual HIV risks. Gilbert L, El-Bassel N, Terlikbayeva A, Rozental Y, Chang M, Brisson A, Wu E, Bakpayev M. Couple-based HIV prevention for injecting drug users in Kazakhstan: A pilot intervention study. *J Prev Interv Community.* 2010; 38(2): 162-176.

Adults and Adolescents Differ On Perceived Effectiveness of Drug Refusal Skills This pilot study examined whether refusal assertion as defined by an evidence-based drug prevention program for youth was associated with adolescent perceptions of effectiveness by comparing two sets of coded responses to adolescent videotaped refusal role-plays (N = 63). The original set of codes was defined by programmatic standards of refusal assertion and the second by a group of high school interns. Consistency with programming criteria was found for interns' ratings of several indicators of verbal and non-verbal assertiveness. However, a refusal skill strategy previously defined by the program as effective--short, simple statements--was perceived as ineffective by adolescent interns while another deemed ineffective and problematic by intervention developers--detailed and reasonable arguments--was viewed as effective. This study suggests the importance of including adolescent perspectives in the design, delivery, and evaluation of drug prevention strategies. The authors argue that including youth perspectives may increase the effectiveness of prevention programs. Nichols T, Birnel S, Graber J, Brooks-Gunn J, Botvin G. Refusal skill ability: An examination of adolescent perceptions of effectiveness. *J Prim Prev.* 2010; 31(3): 127-137.

Portrayals of Smoking in Movies Affects Adolescents' Desire to Smoke

Exposure to smoking in movies is strongly associated with smoking uptake and maintenance among adolescents. However, little is known about what features of movies (e.g., the context for smoking or motives for a character smoking) moderate the association between exposure to movie smoking and adolescent smoking. This laboratory study examined whether exposure to movie smoking that is portrayed as having a clear motive is associated with the desire to smoke differently than smoking that is portrayed as having no clear motive. A sample of 77 middle school students (mean age of 12.8 years, 62% male, 60% Caucasian) viewed movie clips that portrayed smoking as helping to facilitate social interaction, to relax, to appear rebellious, or as having no clear motive. After exposure to each clip, participants rated their desire to smoke. Exposure to clips where smoking was portrayed as helping characters to relax was associated with a significantly stronger desire to smoke compared with clips where the motive for smoking was unclear. Lower levels of desire to smoke occurred for clips where no motive was clear, in social smoking clips, and in

rebellious smoking clips. These results suggest that the way that smoking is portrayed is important in determining its effect on adolescent smoking. Shadel W, Martino S, Haviland A, Setodji C, Primack B. Smoking motives in movies are important for understanding adolescent smoking: A preliminary investigation. *Nicotine Tob Res.* 2010; 12(8): 850-854.

Challenges to Health-Seeking Behavior among Homeless Youth

Approximately 1.5 to 2 million homeless young person's live on the streets in the United States. With the current economic situation, research is needed on quality of services geared toward homeless young adults. The objective of this study was to explore homeless young adults' perspectives on barriers and facilitators of health-care-seeking behavior and their perspectives on improving existing programs for homeless persons. This descriptive qualitative study used focus groups, with a purposeful sample of 24 homeless drug-using young adults. Identified themes were failing access to care based on perceived structural barriers (limited clinic sites, limited hours of operation, priority health conditions, and long wait times) and social barriers (perception of discrimination by uncaring professionals, law enforcement, and society in general). Results provide insight into programmatic and agency resources that facilitate health-seeking behaviors among homeless young adults and include implications for more research with providers of homeless health and social services. Hudson A, Nyamathi A, Greengold B, Slagle A, Koniak-Griffin D, Khalilifard F, Getzoff D. Health-seeking challenges among homeless youth. *Nurs Res.* 2010; 59(3): 212-218.

Concurrent and Longitudinal Predictors of Youth Smoking Behavior and Intention

The concept of "forbidden fruit" has been popularly associated with adolescent cigarette smoking in the US. However, only a few empirical studies have been conducted to investigate how this construct operates among adolescents. The investigators attempted to examine this through the use of a self-report measure that examines youth perceptions of society and their own attitudes toward acceptability of adult versus youth smoking. More than one thousand students from 12 alternative/continuation high schools participated in the study. Students were asked about past 30-day use of cigarettes and smoking intentions. Two "forbidden fruit" constructs were defined through rating scale items such as "Do others in society think it's OK for people your age to smoke?" Participants were measured at baseline and followed up one year later. Some support was found for the theory as one of the forbidden fruit constructs was related to cigarette smoking behavior and intentions. In addition, endorsement of either construct at baseline was related prospectively to smoking intentions in the next 12 months when the analysis was controlled for sensation seeking. Sussman S, Grana R, Pokhrel P, Rohrbach L, Sun P. Forbidden fruit and the prediction of cigarette smoking. *Subst Use Misuse.* 2010; 45 (10): 1683-1693.

Life Stress Increases Risk Behaviors in Cascading Sequence via Link with Negative Emotions

A three-wave cascade model linking life stress to increases in risk behavior was tested with African American emerging adults living in the rural South. Study participants were 347 African American youths (58.5% female) who were in the last 2 years of secondary school at the beginning of the study (M age = 17.7). Data analyses using structural equation modeling and latent growth curve modeling demonstrated that life stress was linked to increases in risk behavior as African Americans transitioned out of secondary school. Youths indicated the number of times during the past month they had used marijuana,

drunk three or more alcoholic beverages (beer, wine, wine coolers, whiskey, gin, or other liquor) at one time, or had sexual intercourse while using substances. Responses to these items were summed to form a past-month risk behavior index. The cascade model indicated that life stress increased negative emotions. Negative emotions, in turn, were linked to increases in affiliations with deviant peers and romantic partners; this forecast increased risk behavior. The findings supported a stress proliferation framework; in which primary stressors affect increases in secondary stressors that carry forward to influence changes in risk behaviors that can potentially compromise mental health. Brody G, Chen Y, Kogan S. A cascade model connecting life stress to risk behavior among rural african american emerging adults. *Dev Psychopathol.* 2010; 22(3): 667-678.

Physiological Measures of Self Regulation as Indicators of Risk for Alcohol Use Problems

This study examined alcohol use behaviors as well as physiological, personality, and motivational measures of arousal in college students approximately 2 years after they were mandated to a brief intervention program for violating university policies about on-campus substance use. This study included 43 university students (51% female; 67% Caucasian, 30% Asian, and 3% other or mixed) who volunteered to participate in a laboratory experiment approximately 2 years after they were mandated to an intervention because they violated university policies about on campus substance use. At the time of the violation, most participants were first-year students (95%) and referred for alcohol-related (95%), rather than drug-related, violations. At the time of the experiment, participants averaged 20.2 years of age (SD=1.0). Participants were categorized based on the seriousness of the referring violation: the minor infraction group (n=30, 70%) included those individuals who were referred by residence hall advisors for being present in a dormitory room where drinking was taking place; the serious infraction group (n=13, 30%) included those individuals whose referral involved emergency medical service or hospital personnel. Self-report measures of arousal, sensation seeking, reasons for drinking, and past 30-day alcohol use were completed. Physiological arousal during exposure to emotional picture cues was assessed by indices of heart rate variability. The minor infraction group reported significantly escalating alcohol use patterns over time and a pattern of less regulated psychophysiological reactivity to external stimuli compared to the serious infraction group. The serious infraction group was higher in sensation seeking and there was some evidence of greater disparity between their physiological and self-reported experiences of emotional arousal in response to picture cues than in the minor group. Thus, the two infraction groups represent different subsets of mandated students, both of whom may be at some risk for maladaptive use of alcohol. The findings suggest that intervention strategies that address self-regulation may be beneficial for mandated college students. Buckman J, White H, Bates M. Psychophysiological reactivity to emotional picture cues two years after college students were mandated for alcohol interventions. *Addict Behav.* 2010; 35(8): 786-790.

The Impact of Relationship Type, Partner Substance Use and Relationship Quality on Drug Behaviors in Young Adulthood

This study used longitudinal data from 909 young adults to examine associations between substance use and the status and quality of romantic relationships. Heavy alcohol use, marijuana use, and cigarette smoking, as well as relationship status, relationship quality, partner substance use, and other salient life circumstances were assessed at four time points in the two years after high school. Marriage, cohabiting relationships, and non-cohabiting dating relationships were associated with reductions in heavy drinking and marijuana use relative to non-dating, after adjusting for adolescent substance use;

marriage compared to not dating was associated with reductions in cigarette smoking. For those in romantic relationships, partner substance use moderated the associations between relationship quality and substance use for heavy drinking and for marijuana use, supporting the hypothesis derived from the Social Development Model that the protective effect of stronger social bonds depends on the use patterns of the partner to whom an individual is bonded. Fleming C, White H, Catalano R. Romantic relationships and substance use in early adulthood: An examination of the influences of relationship type, partner substance use, and relationship quality. *J Health Soc Behav.* 2010; 51 (2): 153-167.

Drug Use and HIV Risk in Hispanic Adolescents: Test of An Ecological Model

Eco-developmental theory is a theoretical framework used to explain the interplay among risk and protective processes associated with HIV risk behaviors among adolescents. Although eco-developmentally based interventions have been found to be efficacious in preventing HIV risk behaviors among Hispanic youth, this theory has not yet been directly empirically tested through a basic research study in this population. The purpose of this cross-sectional study was to empirically evaluate an eco-developmentally based model using structural equation modeling, with substance use and early sex initiation as the two outcomes of the eco-developmental chain of relationships. The sample consisted of 586 Hispanic youth (M age = 13.6; SD = 0.75) and their primary caregivers living in Miami, Florida. Adolescent, parent, and teacher reports were used. The results provided strong support for the theoretical model. Specifically, the parent-adolescent acculturation gap is indirectly related both to early sex initiation and to adolescent substance use through family functioning, academic functioning, perceived peer sexual behavior, and perceived peer substance use. Additionally, parent's U.S. orientation/Americanism is associated with adolescent substance use and adolescent sex initiation through social support for parents, parental stressors, family functioning, academic functioning, and perceived peer sexual behavior and substance use. These findings suggest that HIV risk behaviors may best be understood as associated with multiple and interrelated ecological determinants. Prado G, Huang S, Maldonado-Molina M, Bandiera F, Schwartz S, de la Vega P, Brown C, Pantin H. An empirical test of eco-developmental theory in predicting HIV risk behaviors among hispanic youth. *Health Educ Behav.* 2010; 37 (1): 97-114.

Correlates of Methamphetamine and Other Drug Use in Pregnant American Indian Adolescents

American Indian and Alaska Native adolescents have high rates of pregnancy as well as alcohol, marijuana, cocaine, and methamphetamine use. This study explores correlates of methamphetamine use in a sample of 322 pregnant American Indian youth from four rural reservation communities. Participants were aged 12-19 at the time of conception and data were collected when the youth were between 14 and 35 weeks of gestation. Investigators used both semi-structured and closed ended interview approaches to measure participant drug use, parental alcohol abuse, and teen functioning among other measures. About one quarter of participants reported lifetime use of meth, while lifetime use of alcohol, marijuana, and crack/cocaine were 78%, 75%, and 23% respectively. Almost half of the participants had ever smoked cigarettes. Cigarettes, alcohol, and/or other drugs were used by 25% of participants during pregnancy; the rate of use for individual's substances ranged from 5% for methamphetamine use to 19% for cigarettes. The investigators examined and discussed geographic factors, family related factors, and cultural factors that are correlated with risk for drug use. Barlow A, Mullany BC, Neault N, Davis Y, Billy T, Hastings R, Coho-Mescal V, Lake K, Powers J, Clouse E, Reid R,

Walkup JT. Examining correlates of methamphetamine and other drug use in pregnant American Indian adolescents. *American Indian and Alaska Native Mental Health Research*. 2010; 17 (1): 1-24.

Do HIV+ IDU Recruit Differently from HIV- IDU, Using Respondent-Driven Sampling?

Respondent-driven sampling (RDS) is a network-based method used to recruit hidden populations. Because it is respondent-driven, RDS is prone to bias although these biases could facilitate recruitment of high-risk networks. Recruitment patterns of human immunodeficiency virus (HIV)-positive injection drug users (IDUs) and identified factors associated with being recruited by an HIV-positive IDU in a RDS-based study. IDUs aged $>$ or $=18$, who injected within the last month and resided in Tijuana, Mexico, were recruited using RDS and underwent interviews and testing for HIV, syphilis, and tuberculosis. Weighted logistic regression was used to identify predictors of being recruited by an HIV-positive IDU. Of 1056 IDUs, HIV-positives comprised 4.4% of the sample and generated 4.7% of recruits, indicating that recruitment effectiveness did not vary by HIV-status; however, 10% of the subjects recruited by HIV-positive recruiters were infected with HIV as compared to 4.1% of subjects recruited by HIV-negative recruiters, ($P = 0.06$), a difference that, after controlling for whether the recruiter and recruit injected drugs together, attained statistical significance ($P = 0.04$). This indicated that recruitment patterns differed by HIV-status. Factors independently associated with being recruited by an HIV-positive IDU included lifetime syphilis infection, ever having sex with an HIV-positive person, knowing someone with HIV/AIDS, being recruited at a shooting gallery, having recently used the local needle exchange program, and having a larger number of recent arrests for track marks. Abramovitz D, Volz E, Strathdee S, Patterson T, Vera A, Frost S, Frost S. Using respondent-driven sampling in a hidden population at risk of HIV infection: Who do HIV-positive recruiters recruit?. *Sex Transm Dis*. 2009; 36 (12): 750-756.

Application of Video-Recorded Observations to Assess Implementation Quality

This study used video-recorded observations to assess the implementation quality of Think Smart, a school-based drug prevention curriculum that was designed to reduce use of harmful legal products (HLPs; e.g., inhalants and over-the-counter drugs), alcohol, tobacco, and other drugs among 5th- and 6th-grade students in frontier Alaska. Eight communities that took part in a larger randomized control trial to assess the short-term effects of the Think Smart curriculum participated in this study. Video-recorded observations of the 12 core and 3 booster lessons were conducted in 20 classrooms. Ninety-five sessions were randomly selected from 228 usable videodiscs, and two pairs of researchers observed each video recording to code level of dosage, adherence to curriculum design, and teachers' delivery skills. Inter-rater reliability for all implementation quality measures was very high. An expert panel consisting of 16 scientists reviewed the results of the implementation study and concluded that the level of dosage and adherence to the curriculum design was at least as high as those yielded by similar studies. However, the panel assessed the delivery quality to be only marginal in comparison to results of other studies. The experts concluded that the implementation quality of the Think Smart curriculum was adequate even though the teachers' delivery skills were only marginal. A bootstrapping analysis, in which 1,000 samples were drawn for each implementation quality result, found the expert judgments to be reliable. The authors conclude that despite some limitations, video-recorded observations, as well as expert judgment, provide strong methodologies that should be considered for future implementation quality studies. Johnson K, Ogilvie K, Collins D, Shamblen S, Dirks L, Ringwalt C, Norland J. Studying

implementation quality of a school-based prevention curriculum in frontier Alaska: Application of video-recorded observations and expert panel judgment. *Prev Sci.* 2010; 11 (3): 275-286.

Factors Predicting Arrest and Incarceration among Thai Meth Users

Predictors of arrest and incarceration among Thai methamphetamine users were evaluated through a case control design. Participants were aged 18-25 years old and were a part of a 12 month randomized social network trial. Estimates of the incidence of arrest and incarceration over 12 months were calculated. A matched case-control study (n = 73 cases; n = 223 controls) was performed to examine incarceration risk factors using conditional logistic regression. In total, 35% of the sample reported ever having been arrested and 22% reported ever having been incarcerated at baseline. During the 12 month follow up, 16% of the sample was arrested. In univariate analyses, risk factors for incarceration included frequent drug and alcohol use, being less educated, and a history of arrest and incarceration. A high prevalence of drug and alcohol use and involvement in the drug economy persisted after arrest. Sherman S, Sutcliffe C, Sriroj B, German D, Thomson N, Aramrattana A, Celentano D. Predictors and consequences of incarceration among a sample of young Thai methamphetamine users. *Drug Alcohol Rev.* 2010; 29 (4): 399-405.

European American Parents' Reports on Youth Decision-Making Autonomy Across Middle Childhood and Adolescence

This study addressed three goals: To chart trajectories of global decision making from middle childhood through late adolescence; To examine trajectories of eight decision-making items: appearance, choosing activities, money, social life, bedtime/curfew, chores, homework/schoolwork, and health, and; to test gender, youth's openness to supervision, birth order, and parents' education as potential correlates of decision-making trajectories. Longitudinal patterns of parents' reports on youth decision-making autonomy from ages 9 to 20 were examined in a study of European American families with 2 offspring. The data include 201 firstborn and second-born sibling pairs that entered the study at roughly ages 11 and 9, respectively. Multilevel modeling analyses, which included unconditional polynomial growth models, revealed that decision-making autonomy increased gradually across middle childhood and adolescence before rising sharply in late adolescence. Social domain theory was supported by analyses of 8 decision types spanning prudential, conventional, personal, and multifaceted domains. Decision making was higher for girls, youth whom parents perceived as easier to supervise, and youth with better educated parents. Firstborn and second-born had different age-related trajectories of decision-making autonomy. Findings shed light on the developmental trajectories and family processes associated with adolescents' fundamental task of gaining autonomy. Wray-Lake L, Crouter A, McHale S. Developmental patterns in decision-making autonomy across middle childhood and adolescence: European American parents' perspectives. *Child Dev.* 2010; 81 (2): 636-651.

The Relationship Between High School and College Sports Participation and Substance Use

This study provides an exhaustive review of 34 peer-reviewed quantitative data-based studies completed on high school and college sports involvement and drug use. The studies reviewed suggest that participation in sport is related to higher levels of alcohol consumption, but lower levels of both cigarette smoking and illegal drug use. Additional research is needed in this

domain to further elucidate the relationship between these variables. Lisha N, Sussman S. Relationship of high school and college sports participation with alcohol, tobacco, and illicit drug use: A review. *Addict Behav.* 2010; 35 (5): 399-407.

A Reconceptualization of Acculturation

This article presents an expanded model of acculturation among international migrants and their immediate descendants. Acculturation is proposed as a multidimensional process consisting of the confluence among heritage-cultural and receiving-cultural practices, values, and identifications. The implications of this reconceptualization for the acculturation construct, as well as for its relationship to psychosocial and health outcomes are discussed. In particular, an expanded operationalization of acculturation is needed to address the "immigrant paradox," whereby international migrants with more exposure to the receiving cultural context report poorer mental and physical health outcomes. Authors discuss the role of ethnicity, cultural similarity, and discrimination in the acculturation process, offer an operational definition for context of reception, and call for studies on the role that context of reception plays in the acculturation process. The new perspective on acculturation presented in this article is intended to yield a fuller understanding of complex acculturation processes and their relationships to contextual and individual functioning. Schwartz S, Unger J, Zamboanga B, Szapocznik J. Rethinking The concept of acculturation: Implications for theory and research. *Am Psychol.* 2010; 65 (4): 237-251.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Behavioral and Integrative Treatment Research

Depot Naltrexone Outperforms Oral Naltrexone Except in Severe Heroin Users Treated with Intensive Psychosocial Treatment

A quasi-experimental design was used to combine data from trials on depot and oral naltrexone. Overall, early retention in treatment and urine confirmation of heroin abstinence during the first eight weeks was better for depot naltrexone with one exception; patients with severe heroin use did better on oral naltrexone. These individuals were also participating in an intensive psychosocial treatment. The investigators interpreted this seemingly anomalous finding as the result of the intensity of the psychosocial treatment. This finding is important because it suggests that behavioral treatment may augment outcomes for oral naltrexone even in heroin users with severe dependency. More research is needed to confirm this finding and to examine the combinations of behavioral treatments and medications that work best for subgroups of patients. Brooks AC, Comer SD, Sullivan MA, Bisaga A, Carpenter KM, Raby WM, Yu E, O'Brien CP, Nunes EV. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: A quasi-experiment. *J Clin Psychiatry*. 2010 Oct; 71(10): 1371-1378.

IQ Predicts Coping Skill Acquisition During Computerized Treatment

Coping skills training is an important part of cognitive behavioral therapy (CBT) but drug and alcohol abuse may contribute to cognitive impairment which interferes with learning coping skills. Few studies have examined whether neuropsychological impairment or individual differences in intellectual skills actually impact skill acquisition in psychotherapy. This study examined fifty-two participants randomized to either an eight week computerized CBT skills training program or treatment as usual. Across both treatment conditions, participants who scored above the median on IQ at baseline had greater coping skills acquisition. Additionally, IQ indirectly affected substance use outcomes through an effect on coping skills specifically through those who received the CBT program. This is important because it suggests that improvements in treatment outcome for people with poor cognitive skills may first require remediation of intellectual skills deficits or that existing treatments may require augmentation via various cognitive supports (e.g., reminders, portable memory aids, etc.) in order for the patients to benefit from CBT skills training. Kiluk BD, Nich C, Carroll KM. Relationship of cognitive function and the acquisition of coping skills in computer assisted treatment for substance use disorders. *Drug Alcohol Depend*. 2010 Nov 1. [Epub ahead of print].

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Comparison of Two Intensities of Tobacco Dependence Counseling in Schizophrenia and Schizoaffective Disorder

Compared to the general population, smokers with schizophrenia (SCZ) have reduced success in quitting smoking with usual approaches. This study tested two manualized behavioral counseling approaches, Treatment of Addiction to Nicotine in Schizophrenia (TANS) or Medication Management (MM), for smokers who were motivated to quit. Individual counseling sessions were provided by mental health clinicians in mental health settings, along with nicotine patch. The two treatments varied in intensity and frequency of sessions. Eighty-seven subjects were randomized and attended at least one treatment session. Twenty-one percent (n = 18) of participants had continuous abstinence at 12 weeks after the target quit date, which was not significantly different between conditions (15.6% TANS vs. 26.2% MM, $\chi^2(2) = 1.50$, $p = .221$). Smokers in both groups significantly reduced smoking as measured by cigarettes per day and expired carbon monoxide. Findings support that mental health clinicians can be trained to effectively help smokers with SCZ maintain tobacco abstinence. Williams JM, Steinberg ML, Zimmermann MH, Gandhi KK, Stipelman B, Budsock PD, Ziedonis DM. Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. *J Subst Abuse Treat.* 2010 Jun; 38(4): 384-393.

Relationship Between the Serotonin Transporter Polymorphism and Obsessive-Compulsive Alcohol Craving in Alcohol-Dependent Adults: A Pilot Study

A serotonin deficiency state has been implicated in alcohol-dependent individuals' experience of obsessive-compulsive alcohol craving. Because the serotonin transporter (5-HTT) functions to remove serotonin from the synapse, it is thought that increased reuptake (indicated by the number of high-expressing L(A) alleles present in the 5-HTT gene-linked polymorphic region [5-HTTLPR] of the SLC6A4 gene) is associated with an increase in obsessive-compulsive alcohol craving. The current pilot investigation sought to explore this hypothesis by examining the extent to which obsessive-compulsive alcohol craving varies by 5-HTTLPR genotype among participants enrolled in an ongoing pharmacogenetics trial. All participants were screened with a semi-structured diagnostic interview, completed self-report measures of alcohol-related behavior, and underwent peripheral venous blood draw for DNA genotyping. Cross-sectional data obtained at baseline from 176 currently drinking alcohol-dependent individuals were analyzed using multiple regression. Preliminary findings suggest that 5-HTTLPR is not predictive of Obsessive Compulsive Drinking Scale total and factor scores. Although the 5-HTTLPR polymorphism was not related to obsessive-compulsive alcohol craving in this pilot study, additional research is needed to clarify the possible role of serotonergic mechanisms in alcohol craving. Thompson RD, Heffner JL, Strong JA, Blom TJ, Anthenelli RM. *Alcohol.* 2010 Aug; 44(5): 401-406. Epub 2010 Jul 3.

Gender Differences in the Rates and Correlates of HIV Risk Behaviors among Drug Abusers

This study examined gender differences in the rates and correlates of HIV risk behaviors among 1,429 clients participating in multi-site trials throughout the United States between 2001 and 2005 as part of the National Institute on Drug Abuse-funded Clinical Trials Network. Women engaged in higher risk sexual behaviors. Greater alcohol use and psychiatric severity were associated with higher risk behaviors for women, while impaired social relations were associated with decreased risk for men. Specific risk factors were differentially predictive of HIV risk behaviors for women and men, highlighting the need for

gender-specific risk-reduction interventions. Limitations of the study are discussed. Brooks A, Meade CS, Potter JS, Likhnygina Y, Calsyn DA, Greenfield SF. Gender differences in the rates and correlates of HIV risk behaviors among drug abusers. *Subst Use Misuse*. 2010 Dec; 45(14): 2444-2469.

Multidimensional Family Therapy: Addressing Co-Occurring Substance Abuse and other Problems among Adolescents with Comprehensive Family-Based Treatment

Adolescent substance abuse rarely occurs without other psychiatric and developmental problems, but it is often treated and researched as if it can be isolated from comorbid conditions. Few comprehensive interventions are available that effectively address the range of co-occurring problems associated with adolescent substance abuse. This article reviews the clinical interventions and research evidence supporting the use of Multidimensional Family Therapy (MDFT) for adolescents with substance abuse and co-occurring problems. MDFT is uniquely suited to address adolescent substance abuse and related disorders given its comprehensive interventions that systematically target the multiple interacting risk factors underlying many developmental disruptions of adolescence. Rowe CL. Multidimensional family therapy: Addressing co-occurring substance abuse and other problems among adolescents with comprehensive family-based treatment. *Child Adolesc Psychiatr Clin N Am*. 2010 Jul; 19(3): 563-576.

Prize-Based Contingency Management is Efficacious in Cocaine-Abusing Patients With and Without Recent Gambling Participation

Prize-based contingency management (CM) is efficacious in treating cocaine abuse, and the chance-based procedures of prize CM may be appealing to those who gamble. Using data from three randomized trials, we evaluated whether cocaine-abusing patients who had wagered in the month before treatment ($n = 62$) responded more favorably to prize CM than those who had not ($n = 278$). Participants were randomized to standard care (SC) or SC plus prize CM. Although prize CM was related to better outcomes overall, recent gambling was not associated with outcomes across or within treatment conditions. Gambling participation before treatment entry was associated with reductions in gambling over time, and this effect was more pronounced among those assigned to CM. These data suggest that prize CM is equally efficacious for substance-abusing patients who do and do not gamble, and they extend prior studies indicating that prize CM does not increase gambling. Petry NM, Alessi SM. Prize-based contingency management is efficacious in cocaine-abusing patients with and without recent gambling participation. *J Subst Abuse Treat*. 2010 Oct; 39(3): 282-288.

Psychometric Properties of the Contingency Management Competence Scale

Contingency management (CM) is an evidence-based treatment, and clinicians are beginning to implement this intervention in practice. However, little research exists on methods for assuring appropriate implementation of CM. This study describes the development and psychometric properties of the 12-item CM Competence Scale (CMCS). Thirty-five therapists from nine community-based clinics participated. Following a training period, a randomized trial evaluated the efficacy of CM in cocaine abusing patients. Analyses of the CMCS are based on ratings from 1613 audiotapes of therapist interactions with 78 patients enrolled in the training phase and 103 patients in the randomized phase. Inter-rater reliability from 11 raters and internal consistency of items on the CMCS was good to excellent. Items loaded onto two factors: One contained items specific to discussions of the outcomes of urine testing and

reinforcement, and the other contained general items related to use of praise, communication of confidence, empathy, skillfulness, and maintaining session structure, as well as discussions of self-reports of drug use when they occurred. During the training phase in CM delivery, scores on the CMCS rose significantly between earlier and later training sessions, and during the randomized phase, CM sessions were rated more highly than non-CM sessions. Scores on the subscale assessing general items were significantly correlated with indices of the therapeutic alliance and predictive of durations of cocaine abstinence achieved. These data suggest that the CMCS is reliable and valid in assessing delivery of CM and that competence in CM delivery is associated with improved patient outcomes. Petry NM, Alessi SM, Ledgerwood DM, Sierra S. Psychometric properties of the contingency management competence scale. *Drug Alcohol Depend.* 2010 Jun 1; 109(1-3): 167-174.

Effect of Incarceration History on Outcomes of Primary Care Office-Based Buprenorphine/ Naloxone

Behaviors associated with opioid dependence often involve criminal activity, which can lead to incarceration. The impact of a history of incarceration on outcomes in primary care office-based buprenorphine/naloxone is not known. The purpose of this study is to determine whether having a history of incarceration affects response to primary care office-based buprenorphine/naloxone treatment. In this post hoc secondary analysis of a randomized clinical trial, we compared demographic, clinical characteristics, and treatment outcomes among 166 participants receiving primary care office-based buprenorphine/naloxone treatment stratifying on history of incarceration. Participants with a history of incarceration have similar treatment outcomes with primary care office-based buprenorphine/naloxone than those without a history of incarceration (consecutive weeks of opioid-negative urine samples, 6.2 vs. 5.9, $p = 0.43$; treatment retention, 38% vs. 46%, $p = 0.28$). Prior history of incarceration does not appear to impact primary care office-based treatment of opioid dependence with buprenorphine/ naloxone. Community health care providers can be reassured that initiating buprenorphine/naloxone in opioid dependent individuals with a history of incarceration will have similar outcomes as those without this history. Wang EA, Moore BA, Sullivan LE, Fiellin DA. Effect of incarceration history on outcomes of primary care office-based buprenorphine/naloxone. *J Gen Intern Med.* 2010 Jul; 25(7): 670-674.

Effect of Anxiety on Treatment Presentation and Outcome: Results from the Marijuana Treatment Project

Despite emerging evidence of the efficacy of psychotherapies for marijuana dependence, variability in outcome exists. This study examined the role of anxiety on treatment involvement and outcome. Four questions were examined: (1) Is greater anxiety associated with greater impairment at baseline? (2) Is baseline anxiety related to greater marijuana use and problems following treatment? (3) Does adding cognitive-behavioral therapy (CBT) to motivation enhancement therapy (MET) reduce anxiety relative to MET alone; (4) Are reductions in anxiety associated with better outcomes? The sample comprised 450 marijuana-dependent patients in the Marijuana Treatment Project. Marijuana use and anxiety were measured at pretreatment and 4- and 9-month follow-ups. At baseline, anxiety was linked to more marijuana-related problems. CBT was associated with less anxiety at follow-up compared to MET alone. Reductions in anxiety were related to less marijuana use. In fact, reduction in anxiety from baseline to 4-month follow-up was associated with less marijuana use at 9 months, but reduction in marijuana use did not predict subsequent anxiety. Data suggest that anxiety is an important variable that deserves further attention in marijuana-dependence treatment. Buckner JD, Carroll KM. Effect of anxiety on treatment presentation and

outcome: Results from the Marijuana Treatment Project. *Psychiatry Res.* 2010 Aug 15; 178(3): 493-500.

Effect of Binge Eating on Treatment Outcomes for Smoking Cessation

This study investigated the effect of binge eating on smoking cessation outcomes. Participants (n = 186) reported binge eating status at baseline and at a 6-week postquit evaluation during a larger clinical trial for smoking cessation. Binge eating was defined with a single self-report questionnaire item from the Dieting and Bingeing Severity Scale. Participant groups defined by binge eating status were compared on abstinence rates. Among participants, 22% reported binge eating at baseline, 17% denied binge eating at baseline but endorsed binge eating by 6 weeks, and 61% denied binge eating at both time points. Participants who reported binge eating prior to or during treatment had lower quit rates at 6-week postquit and at the 24-week follow-up point than those without binge eating. The groups did not differ at the 12-week follow-up point. The group that experienced an emergence of binge eating reported significantly more weight gain than the other groups. These results suggest that treatments addressing problematic eating behaviors during smoking cessation are warranted. White MA, Peters EN, Toll BA. Effect of binge eating on treatment outcomes for smoking cessation. *Nicotine Tob Res.* 2010 Nov; 12(11): 1172-1175.

"Everyone Deserves Services No Matter What": Defining Success In Harm-Reduction-Based Substance User Treatment

This article reports qualitative interview data from a study of participant-generated outcomes of two harm reduction programs in the United States. We address the question: "What does success in harm-reduction-based substance user treatment look like?" Providers in this study understood harm reduction to adhere to notions of "any positive change," client centeredness, and low-threshold services. Participants reported changes in demarginalization, engagement in the program, quality of life, social functioning, changes in substance use, and changes in future goals and plans. The nature of these changes is difficult to articulate within traditional notions of success (i.e., abstinence, program completion, etc.). We conclude that participants in harm reduction programs experience tangible positive changes but that legitimization of these changes calls for a reconceptualization of "outcomes" and "success" in the current context of substance user treatment and research. Lee HS, Zerai A. "Everyone deserves services no matter what": defining success in harm-reduction-based substance user treatment. *Subst Use Misuse.* 2010 Dec; 45(14): 2411-2427.

HIV Risk Behavior in Treatment-Seeking Opioid-Dependent Youth

The purpose of this study was to assess changes in HIV drug and sexual risk behavior in youth receiving treatment for opioid dependence. One hundred fifty participants were randomly assigned to extended buprenorphine/naloxone therapy (BUP) + drug counseling for 12 weeks or detoxification for 2 weeks + drug counseling for 12 weeks. HIV risk was assessed at baseline and 4-week, 8-week, and 12-week follow-ups. Behavioral change was examined using generalized estimating equations. Findings indicate that IDU decreased over time ($p < 0.001$), with greater decreases in BUP versus detoxification ($p < 0.001$) and females versus males in BUP ($p < 0.05$). Injection risk did not change for persistent injectors. Sexual activity decreased in both genders and conditions ($p < 0.01$), but sexual risk did not. The authors conclude that, although IDU and sexual activity decreased markedly as a function of treatment, particularly in BUP patients and females, risk reduction counseling

may be necessary to extend its benefits. Meade CS, Weiss RD, Fitzmaurice GM, Poole SA, Subramaniam GA, Patkar AA, Connery HS, Woody GE. HIV risk behavior in treatment-seeking opioid-dependent youth: results from a NIDA clinical trials network multisite study. *J Acquir Immune Defic Syndr*. 2010 Sep 1; 55(1): 65-72.

Greater Risk Associated with Opioid Problem Use Among Youth with Marijuana and Alcohol Problem Use

This study assessed the added risk of opioid problem use (OPU) in youth with marijuana/alcohol problem use (MAPU). A total of 475 youth (ages 14-21 years) with OPU + MAPU were compared to a weighted sample of 475 youth with MAPU only (i.e. no OPU) before and after propensity score matching on gender, age, race, level of care and weekly use of marijuana/alcohol. Youth were recruited from 88 drug treatment sites participating in eight Center for Substance Abuse Treatment-funded grants. At treatment intake, participants were administered the Global Appraisal of Individual Need to elicit information on demographic, social, substance, mental health, human immunodeficiency virus (HIV), physical and legal characteristics. Odds ratios with confidence intervals were calculated. The added risk of OPU among MAPU youth was associated with higher rates of psychiatric symptoms and trauma/victimization, greater HIV risk behaviors, and greater physical distress. The OPU + MAPU group was more likely to be 15-17 years old, Caucasian, report weekly drug use at home and among peers, engage in illegal behaviors and more severe consequences, have greater substance abuse severity and polydrug use, and use mental health and substance abuse treatment services. These findings highlight the substantial incremental risk of OPU on multiple comorbid areas among treatment-seeking youth. The authors conclude that further evaluation is needed to assess their outcomes following standard drug treatment and to evaluate specialized interventions for this subgroup of severely impaired youth. Subramaniam GA, Ives ML, Stitzer ML, Dennis ML. The added risk of opioid problem use among treatment-seeking youth with marijuana and/or alcohol problem use. *Addiction*. 2010 Apr; 105(4): 686-698.

Cost-Effectiveness of Extended Buprenorphine-Naloxone Treatment for Opioid-Dependent Youth

The purpose of this study was to estimate cost, net social cost and cost-effectiveness in a clinical trial of extended buprenorphine-naloxone (BUP) treatment versus brief detoxification treatment in opioid-dependent youth. Economic evaluation of a clinical trial was conducted at six community out-patient treatment programs from July 2003 to December 2006, which were randomized to 12 weeks of BUP or a 14-day taper (DETOX). BUP patients were prescribed up to 24 mg per day for 9 weeks and then tapered to zero at the end of week 12. DETOX patients were prescribed up to 14 mg per day and then tapered to zero on day 14. All were offered twice-weekly drug counseling. Participants included 152 patients aged 15-21 years. Data were collected prospectively during the 12-week treatment and at follow-up interviews at months 6, 9 and 12. The 12-week out-patient study treatment cost was \$1514 ($P < 0.001$) higher for BUP relative to DETOX. One-year total direct medical cost was only \$83 higher for BUP ($P = 0.97$). The cost-effectiveness ratio of BUP relative to DETOX was \$1376 in terms of 1-year direct medical cost per quality-adjusted life year (QALY) and \$25,049 in terms of out-patient treatment program cost per QALY. The acceptability curve suggests that the cost-effectiveness ratio of BUP relative to DETOX has an 86% chance of being accepted as cost-effective for a threshold of \$100,000 per QALY. The authors conclude that extended BUP treatment relative to brief detoxification is cost effective in the US health-care system for the outpatient treatment of opioid-dependent youth. Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of extended buprenorphine-naloxone treatment

for opioid-dependent youth: data from a randomized trial. *Addiction*. 2010 Sep; 105(9): 1616-1624.

Screening for Prenatal Substance Use: Development of the Substance Use Risk Profile-Pregnancy Scale

The authors report on the development of a questionnaire to screen for hazardous substance use in pregnant women and to compare the performance of the questionnaire with other drug and alcohol measures. In this study, pregnant women were administered a modified TWEAK (Tolerance, Worried, Eye-openers, Amnesia, K[C] Cut Down) questionnaire, the 4Ps Plus questionnaire, items from the Addiction Severity Index, and two questions about domestic violence (N=2,684). The sample was divided into "training" (n=1,610) and "validation" (n=1,074) subsamples. The authors applied recursive partitioning class analysis to the responses from individuals in the training subsample that resulted in a three-item Substance Use Risk Profile-Pregnancy scale. They examined sensitivity, specificity, and the fit of logistic regression models in the validation subsample to compare the performance of the Substance Use Risk Profile-Pregnancy scale with the modified TWEAK and various scoring algorithms of the 4Ps. Results indicated that the Substance Use Risk Profile-Pregnancy scale was comprised of three informative questions that can be scored for high- or low-risk populations. The Substance Use Risk Profile-Pregnancy scale algorithm for low-risk populations was mostly highly predictive of substance use in the validation subsample (Akaike's Information Criterion=579.75, Nagelkerke R=0.27) with high sensitivity (91%) and adequate specificity (67%). The high-risk algorithm had lower sensitivity (57%) but higher specificity (88%). In sum, the Substance Use Risk Profile-Pregnancy scale is simple and flexible with good sensitivity and specificity. The Substance Use Risk Profile-Pregnancy scale can potentially detect a range of substances that may be abused. Clinicians need to further assess women with a positive screen to identify those who require treatment for alcohol or illicit substance use in pregnancy. Yonkers KA, Gotman N, Kershaw T, Forray A, Howell HB, Rounsaville BJ. Screening for prenatal substance use: development of the Substance Use Risk Profile-Pregnancy scale. *Obstet Gynecol*. 2010 Oct; 116(4): 827-833.

Informal Care and Reciprocity of Support are Associated with HAART Adherence Among Men in Baltimore, MD

Research suggests gender differences in interpersonal relationship factors important to health. This study examined relationship factors associated with HAART adherence among men. The sample (n = 154) comprised 95% African Americans and 48% current illicit drug users; 83% reported HAART adherence. Results revealed adherence was associated with comfort level taking HAART in the presence of close friends, and the interaction between informal care (having someone to care for oneself when sick in bed) and reciprocity of support. Among those with informal care, higher reciprocity of support to caregivers was associated with greater adherence. Promoting men's reciprocity of support to their caregivers and enhancing peer norms of medication taking are important strategies for improving men's adherence. The findings complement previous findings on relationship factors adversely associated with women's adherence. Results suggest the merit of interventions targeting men and their informal caregivers, particularly main partners, and gender-specific, contextually tailored strategies to promote HAART adherence. Knowlton AR, Yang C, Bohnert A, Wissow L, Chander G, Arnsten JA. Informal care and reciprocity of support are associated with HAART adherence among men in Baltimore, MD, USA. *AIDS Behav*. 2010 Jul 15. [Epub ahead of print].

Anxiety Sensitivity and Illicit Sedative Use Among Opiate-

Dependent Women and Men

Research has suggested that individuals with elevated anxiety sensitivity (AS, the fear of benign bodily sensations associated with anxiety) are more likely to use substances to cope with distress, particularly substances with arousal-dampening effects such as benzodiazepines and other sedatives. Such coping motives may also vary as a function of gender, with women more likely to use substances for coping (self-medicating) purposes. Given these findings, the authors hypothesized that AS would be associated with illicit sedative use in an opioid-dependent sample and that gender would moderate this relationship, with a greater association among women. Participants were 68 opioid-dependent patients recruited from a methadone maintenance clinic. A logistic regression was used to determine whether AS was associated with presence or absence of a history of illicit sedative use. Results indicated that AS was significantly associated with sedative use and this relationship was moderated by gender; elevated AS was associated with greater sedative use only in women. In sum, the presence of elevated AS is related to greater illicit use of sedatives in women but not in men. Women may be more susceptible to seeking sedatives as a means of coping with unpleasant, anxious sensations. Hearon BA, Calkins AW, Halperin DM, Kathryn McHugh R, Murray HW, Otto MW. Anxiety sensitivity and illicit sedative use among opiate-dependent women and men. *Am J Drug Alcohol Abuse*. 2010 Nov 19. [Epub ahead of print]

Anxiety Disorders Among Methamphetamine Dependent Adults: Association with Post-Treatment Functioning

Although anxiety is one of the most prominent psychiatric complaints of methamphetamine (MA) users, little is known about the association between anxiety disorders and treatment outcomes in this population. Using data from 526 adults in the largest psychosocial clinical trial of MA users conducted to date, this study examined psychiatric, substance use, and functional outcomes of MA users with concomitant anxiety disorders 3 years after treatment. Anxiety disorders were associated with poorer alcohol and drug use outcomes, increased health service utilization, and higher levels of psychiatric symptomatology, including suicidality. Addressing anxiety symptoms and syndromes in MA users may be helpful as a means of optimizing treatment outcomes. Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson R, Methamphetamine Treatment Project Corporate Authors. Anxiety disorders among methamphetamine dependent adults: association with post-treatment functioning. *Am J Addict*. 2010 Sep; 19(5): 385-390.

A Systematic Review of the Impact of Alcohol Use Disorders on HIV Treatment Outcomes, Adherence to Antiretroviral Therapy and Health Care Utilization

Alcohol use disorders (AUDs) are highly prevalent and associated with non-adherence to antiretroviral therapy, decreased health care utilization and poor HIV treatment outcomes among HIV-infected individuals. In this study, the authors systematically reviewed studies assessing the impact of AUDs on: (1) medication adherence, (2) health care utilization and (3) biological treatment outcomes among people living with HIV/AIDS (PLWHA). Six electronic databases and Google Scholar were queried for articles published in English, French and Spanish from 1988 to 2010. Selected references from primary articles were also examined. Selection criteria included: (1) AUD and adherence (N=20); (2) AUD and health services utilization (N=11); or (3) AUD with CD4 count or HIV-1 RNA treatment outcomes (N=10). Reviews, animal studies, non-peer reviewed documents and ongoing studies with unpublished data were excluded. Studies that did not differentiate HIV+ from HIV- status and those that did not distinguish between drug and alcohol use were also

excluded. Data were extracted, appraised and summarized. The findings consistently support an association between AUDs and decreased adherence to antiretroviral therapy and poor HIV treatment outcomes among HIV-infected individuals. Their effect on health care utilization, however, was variable. Azar MM, Springer SA, Meyer JP, Altice FL. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend*. 2010 Aug 10. [Epub ahead of print].

Directly Observed Antiretroviral Therapy in Substance Abusers Receiving Methadone Maintenance Therapy Does Not Cause Increased Drug Resistance

Direct observation of antiretroviral therapy (DOT) can increase adherence rates in HIV-infected substance users, but whether this affects the development of antiretroviral drug resistance has not been fully explored. The authors conducted a 24-week randomized controlled trial of methadone clinic-based antiretroviral DOT compared with treatment as usual (TAU) among antiretroviral-experienced substance users. To examine the development of new resistance mutations, the authors identified all participants with an amplifiable resistance test at both baseline and either week 8 or week 24 and compared the development of new drug resistance mutations between participants in the two arms of the trial. Among the 77 participants enrolled in the parent trial, antiretroviral DOT was efficacious for improving adherence and decreasing HIV viral load. Twenty-one participants had a detectable HIV viral load at both baseline and a second time point. Of these, nine developed new drug resistance mutations not seen at baseline (three in the DOT arm and six in the TAU arm; $p = 0.27$). Overall, five subjects in the TAU arm developed major mutations correlating with their current antiretroviral regimen, while no subjects in the DOT arm developed such mutations. Direct observation of antiretroviral therapy was associated with improved adherence and viral suppression among methadone maintained HIV-infected substance users, but was not associated with an increase in the development of antiretroviral drug resistance. DOT should be considered for substance users attending methadone maintenance clinics who are at high risk of nonadherence. Brust JC, Litwin AH, Berg KM, Li X, Heo M, Arnsten JH. Directly observed antiretroviral therapy in substance abusers receiving methadone maintenance therapy does not cause increased drug resistance. *AIDS Res Hum Retroviruses*. 2010 Nov 23. [Epub ahead of print].

Directly Observed Antiretroviral Therapy Improves Adherence and Viral Load in Drug Users Attending Methadone Maintenance Clinics

In this two-group randomized trial the authors sought to determine if directly observed antiretroviral therapy (DOT) is more efficacious than self-administered therapy for improving adherence and reducing HIV viral load (VL) among methadone-maintained opioid users. Participants included HIV-infected adults prescribed combination antiretroviral therapy at twelve methadone maintenance clinics with on-site HIV care in the Bronx, New York. Between June 2004 and August 2007, the authors enrolled 77 participants. Adherence in the DOT group was higher than in the control group at all post-baseline assessment points; by week 24 mean DOT adherence was 86% compared to 56% in the control group ($p < 0.0001$). Group differences in mean adherence remained significant after stratifying by baseline VL (detectable versus undetectable). In addition, during the 24-week intervention, the proportion of DOT participants with undetectable VL increased from 51% to 71%. Main results indicated between group differences at four assessment points from baseline to week 24 in: (1) antiretroviral adherence measured by pill count, (2)

VL, and (3) proportion with undetectable VL (<75copies/ml). In sum, among HIV-infected opioid users, antiretroviral DOT administered in methadone clinics was efficacious for improving adherence and decreasing VL, and these improvements were maintained over a 24-week period. DOT should be more widely available to methadone patients. Berg KM, Litwin A, Li X, Heo M, Arnsten JH. Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: A randomized controlled trial. *Drug Alcohol Depend*. 2010 Sep 8. [Epub ahead of print].

Changes in Coping Moderate Substance Abuse Outcomes Differentially across Behavioral Treatment Modality

In this secondary data analytic study, the authors examined whether the relationship between changes in coping and treatment outcome differed between women enrolled in either the Women's Recovery Group (WRG) (n = 29), a new manualized group treatment for women with substance use disorders, or Group Drug Counseling (GDC) (n = 7), an empirically supported mixed-gender group treatment. The authors examined subscales of the Ways of Coping Questionnaire and found that while changes in coping did not differ significantly across treatment groups, the association between changes in coping and substance abuse outcome was related to treatment condition. Increases in problem-focused coping were associated with decreased drinking days in WRG, but paradoxically with increased drinking days in GDC. For both groups, increases in wishful thinking were associated with increases in substance use, and increases in social support coping associated with decreases in use, but these associations were greater in GDC. The results highlight the importance of examining the impact of treatment modality on coping, as well as contextual factors that may help to explain the specific pattern of results. Kuper LE, Gallop R, Greenfield SF. Changes in coping moderate substance abuse outcomes differentially across behavioral treatment modality. *Am J Addict*. 2010 Nov; 19(6): 543-549.

Longitudinal Predictors of Addictions Treatment Utilization in Treatment-Na•ve Adults with Alcohol Use Disorders

Despite the substantial prevalence of alcohol use disorders (AUDs), prior research indicates that most people with AUDs never utilize either formal or informal treatment services. Several prior studies have examined the characteristics of individuals with AUDs who receive treatment; however, limited longitudinal data are available on the predictors of receiving AUD services in treatment-naive individuals with AUDs. This study utilized data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) to identify adults in Wave 1 who met criteria for an AUD within the last 12 months and reported no prior lifetime alcohol treatment (N=2760). These individuals were surveyed again at Wave 2, approximately 3-4 years later (N=2170). This study examined the Wave 1 demographic and psychiatric conditions that were associated with receipt of AUD treatment services between Waves 1 and 2. In multivariable analyses, use of AUD treatment services between Waves 1 and 2 was significantly more likely among those who were male, non-Caucasian, younger, had lower income, and who had health insurance. Additionally, those who met criteria for a baseline drug use disorder, anxiety disorder or a personality disorder were more likely to receive AUD treatment. In sum, treatment was more often utilized in those who had more severe baseline psychopathology and in those with fewer economic resources. These findings highlight the need to broaden the types of care available to individuals with AUDs to increase the appeal of AUD services. Ilgen MA, Price AM, Burnett-Zeigler I, Perron B, Islam K, Bohnert AS, Zivin K. Longitudinal predictors of addictions treatment utilization in treatment-na•ve adults with alcohol use disorders. *Drug Alcohol Depend*. 2010 Sep 7. [Epub ahead of

print].

Remember the Future: Working Memory Training Decreases Delay Discounting among Stimulant Addicts

Excessive discounting of future rewards has been observed in a variety of disorders and has been linked both to valuation of the past and to memory of past events. To explore the functionality of discounting and memory, Dr. Bickel and colleagues examined whether training of working memory would result in less discounting of future rewards. In this study, 27 adults in treatment for stimulant use were randomly assigned to receive either working memory training or control training according to a yoked experimental design. Measures of delay discounting and several other cognitive behaviors were assessed pre- and post-training. Results suggest that rates of discounting of delayed rewards were significantly reduced among those who received memory training but were unchanged among those who received control training; other cognitive assessments were not affected by memory training. Discount rates were positively correlated with memory training performance measures. To our knowledge, this is the first study demonstrating that neurocognitive training on working memory decreases delay discounting. These results offer further evidence of a functional relationship between delay discounting and working memory. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: Working Memory training decreases delay discounting among stimulant addicts. *Biol Psychiatry*. 2010 Oct 19. [Epub ahead of print].

The Association between Cocaine Use and Treatment Outcomes in Patients Receiving Office-based Buprenorphine/Naloxone for the Treatment of Opioid Dependence

Cocaine use in patients receiving methadone is associated with worse treatment outcomes. The association between cocaine use and office-based buprenorphine/naloxone treatment outcomes is not known. Dr. Sullivan and colleagues at Yale University evaluated the association between baseline and in-treatment cocaine use, treatment retention, and urine toxicology results in 162 patients enrolled in a 24-week trial of primary care office-based buprenorphine/naloxone maintenance. Patients with baseline cocaine metabolite-negative urine toxicology tests compared with those with cocaine metabolite-positive tests had more mean weeks of treatment retention (18.3 vs. 15.8, $p = .04$), a greater percentage completed 24 weeks of treatment (50% vs. 33%, $p = .04$) and had a greater percentage of opioid-negative urines (47% vs. 34%, $p = .02$). Patients with in-treatment cocaine metabolite-negative urine toxicology tests compared with cocaine metabolite-positive patients had more mean weeks of treatment retention (19.0 vs. 16.5, $p = .003$), a greater percentage completed 24 weeks of treatment (60% vs. 30%, $p < .001$), and had a greater percentage of opioid-negative urines (51% vs. 35%, $p = .001$). The authors conclude that both baseline and in-treatment cocaine use is associated with worse treatment outcomes in patients receiving office-based buprenorphine/ naloxone and may benefit from targeted interventions. Sullivan LE, Moore BA, O'Connor PG, Barry DT, Chawarski MC, Schottenfeld RS, Fiellin DA. The association between cocaine use and treatment outcomes in patients receiving office-based buprenorphine/naloxone for the treatment of opioid dependence. *Am J Addict*. 2010 Jan-Feb; 19(1): 53-58.

Voucher Incentives Increase Treatment Participation in Telephone-based Continuing Care for Cocaine Dependence

Telephone-based monitoring is a promising approach to continuing care of substance use disorders, but patients often do not engage or participate enough to benefit. Voucher incentives can increase retention in outpatient

treatment and continuing care, but may be less effective when reinforcement is delayed, as in telephone-based care. Dr. McKay and colleagues from the University of Pennsylvania compared treatment utilization rates among cocaine-dependent patients enrolled in telephone continuing care with and without voucher incentives to determine whether incentives increase participation in telephone-based care. Participants were 195 cocaine-dependent patients who completed two weeks of community-based intensive outpatient treatment for substance use disorders and were randomly assigned to receive telephone continuing care with or without voucher incentives for participation as part of a larger clinical trial. The 12-month intervention included 2 in-person orientation sessions followed by up to 30 telephone sessions. Incentivized patients could receive up to \$400 worth of gift cards. Results show that patients who received incentives were not more likely to complete their initial orientation to continuing care. Incentivized patients who completed orientation completed 67% of possible continuing care sessions, as compared to 39% among non-incentivized patients who completed orientation. Among all patients randomized to receive incentives, the average number of completed sessions was 15.5, versus 7.2 for patients who did not receive incentives, and average voucher earnings were \$200. Voucher incentives can have a large effect on telephone continuing care participation, even when reinforcement is delayed. Further research will determine whether increased participation leads to better outcome among patients who received incentives. Van Horn DH, Drapkin M, Ivey M, Thomas T, Domis SW, Abdalla O, Herd D, McKay JR. Voucher incentives increase treatment participation in telephone-based continuing care for cocaine dependence. *Drug Alcohol Depend.* 2010 Oct 30. [Epub ahead of print].

Effects of Smoking Cessation on Body Composition in Postmenopausal Women

Investigators at the University of Connecticut conducted this study to evaluate the effects of smoking cessation on measures of body composition (BC). The effects of 16 months of cigarette abstinence on areas of BC measured by dual-energy x-ray absorptiometry (DXA) were examined. One hundred fifty-two postmenopausal women participated in a smoking cessation study using the nicotine patch. Secondary analyses were conducted on data from 119 subjects who had had DXA scans at baseline and 16 months later. Participants were classified either as quitters (self-reported cigarette abstinence confirmed with exhaled carbon monoxide at 3 and 16 months after quit date) or as continued smokers. Four areas of BC (kg) were measured: Whole body weight, fat mass, muscle mass, and functional skeletal muscle mass in arms and legs. The results indicated that quitters significantly increased body weight ($p < 0.001$), fat mass (< 0.001), muscle mass ($p = 0.04$), and functional muscle mass ($p = 0.004$) over time, when baseline BC measures and other confounding factors were controlled. Analysis indicated change in BC could not be accounted for by calorie intake or physical activity. The authors concluded that smoking cessation may be associated with increased fat and muscle mass in postmenopausal women. The novel finding of an increase in functional muscle mass suggests that smoking cessation could increase functional capacity. Further studies need to replicate these findings and examine mechanisms of these effects. Kleppinger A, Litt MD, Kenny AM, Oncken CA. Effects of smoking cessation on body composition in postmenopausal women. *J Womens Health (Larchmt).* 2010 Sep; 19(9): 1651-1657.

Mechanisms of Change in Extended Cognitive Behavioral Treatment for Tobacco Dependence

Investigators at the University of California, San Francisco conducted this study to evaluate potential mediators of an extended cognitive behavioral smoking cessation intervention. Data were analyzed from a randomized clinical trial of

smoking cessation. Participants were older cigarette smokers (≥ 50 years old). Receiving either Standard Treatment (N=100) or extended cognitive behavioral treatment (N=99). All were measured at the beginning of treatment and week 52. Analyses revealed that extended CBT increased abstinence self-efficacy over the first 52 weeks postcessation. This effect, in turn, was positively associated with 7-day point prevalence abstinence at week 64 while controlling for treatment condition, and eliminated the independent effect of treatment condition on abstinence. The test of mediation indicated a significant effect, and abstinence self-efficacy accounted for 61% to 83% of the total effect of treatment condition on smoking abstinence. Results failed to support a mediational role of negative affect, abstinence-specific social support, or motivation to quit. The results of the present study are consistent with theories of relapse and studies of more time-limited interventions, and underscore the importance of abstinence self-efficacy in achieving long-term abstinence from cigarettes. Hendricks PS, Delucchi KL, Hall SM. Mechanisms of change in extended cognitive behavioral treatment for tobacco dependence. *Drug Alcohol Depend.* 2010 Jun 1; 109(1-3): 114-119.

Failure to Treat Tobacco Use in Mental Health and Addiction Treatment Settings: A Form of Harm Reduction?

In mental health and addiction treatment settings, failure to treat tobacco dependence has been rationalized by some as a clinical approach to harm reduction. That is, tobacco use is viewed as a less harmful alternative to alcohol or illicit drug use and/or other self-harm behaviors. In this paper, Dr. Prochaska from the University of California, San Francisco, examines the impact of providers' failure to treat tobacco use on patients' alcohol and illicit drug use and associated high-risk behaviors. The weight of the evidence in the literature indicates: (1) tobacco use is a leading cause of death in patients with psychiatric illness or addictive disorders; (2) tobacco use is associated with worsened substance abuse treatment outcomes, whereas treatment of tobacco dependence supports long-term sobriety; (3) tobacco use is associated with increased (not decreased) depressive symptoms and suicidal risk behavior; (4) tobacco use adversely impacts psychiatric treatment; (5) tobacco use is a lethal and ineffective long-term coping strategy for managing stress, and (6) treatment of tobacco use does not harm mental health recovery. Failure to treat tobacco dependence in mental health and addiction treatment settings is not consistent with a harm reduction model. In contrast, emerging evidence indicates treatment of tobacco dependence may even improve addiction treatment and mental health outcomes. Providers in mental health and addiction treatment settings have an ethical duty to intervene on patients' tobacco use and provide available evidence-based treatments. Prochaska JJ. Failure to treat tobacco use in mental health and addiction treatment settings: A form of harm reduction? *Drug Alcohol Depend.* 2010 Aug 1; 110(3): 177-182.

Reaching Young Adult Smokers through the Internet: Comparison of Three Recruitment Mechanisms

While young adults have the highest prevalence of cigarette smoking of any adult age group, studies of tobacco and other substance use have reported challenges in recruiting this age group. The Internet may be a useful tool for reaching young adult smokers. Investigators from the University of California, San Francisco conducted the present study to compare three Internet-based recruitment methods for young adult smokers to complete a survey about tobacco and other substance use: Craigslist advertisements, other Internet advertisements, and E-mail invitations through a survey sampling service. Recruitment campaigns invited young adults aged 18-25 years who had smoked at least one cigarette in the past 30 days to complete an online survey. Recruitment methods were compared across recruitment numbers, cost

effectiveness, and demographic and smoking characteristics of recruited participants. The results showed that in 6 months, 920 people gave online consent to determine eligibility to complete the survey, of which 336 (36.5%) were eligible, and 201 (59.8%) completed the survey. While Internet advertisements yielded the largest proportion of recruited participants and completed surveys overall, Craigslist and sampling strategies were more successful at targeting young adult smokers who went on to complete the survey and were more cost effective. Participants differed in demographic and substance use characteristics across the three recruitment mechanisms. The researchers were successful at reaching young adults who have smoked cigarettes recently through the Internet, though costs, participant eligibility, proportion of completed surveys, and respondent characteristics differed among the three methods. A multipronged approach to Internet recruitment is most likely to generate a broad diverse sample of young adult smokers. Ramo DE, Hall SM, Prochaska JJ. Reaching young adult smokers through the internet: Comparison of three recruitment mechanisms. *Nicotine Tob Res.* 2010 Jul; 12(7): 768-775.

OROS-Methylphenidate or Placebo for Adult Smokers with Attention Deficit Hyperactivity Disorder: Racial/Ethnic Differences

Investigators at Columbia University conducted this study to explore racial/ethnic difference in the efficacy of OROS-methylphenidate (OMPH), a treatment for ADHD, as an adjunctive medication for improving cessation rates among smokers with attention deficit hyperactivity disorder (ADHD). Participants were adult smokers with ADHD (202 whites and 51 non-whites) randomly assigned to OMPH or placebo in a multi-site, randomized controlled trial. Study outcomes were complete, prolonged, and point-prevalence abstinence at the end of treatment, and weekly ratings of ADHD symptoms, tobacco withdrawal symptoms, and desire to smoke. The rate of four-week complete abstinence (no slips or lapses) was significantly higher with OMPH than placebo among non-white (OMPH=42.9%, placebo=13.3%) but not white participants (OMPH=23.1%, placebo=23.5%). Patterns of prolonged and point-prevalence abstinence among non-whites were similar but fell short of statistical significance. OMPH reduced ADHD symptoms in both race/ethnic groups, and produced greater reductions in desire to smoke and withdrawal symptoms among the non-white than white participants. Change in desire to smoke, but not in withdrawal or ADHD symptoms predicted abstinence. The ability of OMPH to reduce desire to smoke among non-whites appeared to mediate the medication's positive effect on abstinence. Differential efficacy favoring non-whites of a medication for achieving smoking cessation is a potentially important finding that warrants further investigation. OROS-MPH could be an effective treatment for nicotine dependence among a subgroup of smokers. Covey LS, Hu MC, Winhusen T, Weissman J, Berlin I, Nunes EV. OROS-methylphenidate or placebo for adult smokers with attention deficit hyperactivity disorder: Racial/ethnic differences. *Drug Alcohol Depend.* 2010 Jul 1; 110(1-2): 156-159.

Cigarette Smoking Knowledge, Attitudes, and Practices of Patients and Staff at a Perinatal Substance Abuse Treatment Center

This study, conducted by investigators at Johns Hopkins University, compares cigarette smoking knowledge, attitudes, and practices (S-KAP) of opioid- and other substance-dependent patients and their multidisciplinary staff at an outpatient perinatal substance abuse treatment center. Consenting patients (n = 95) and staff (n = 41) concurrently completed a modified form of the S-KAP survey instrument. Ninety-five percent of patients reported currently smoking, and half endorsed wanting "to quit smoking now." This patient desire to quit smoking was significantly underrated by staff compared to the patients

themselves ($p = .028$). Both patients and staff demonstrated suboptimal knowledge of smoking health risks, but 73% of patients reported trying to quit with past pregnancies to avoid harm to the fetus/baby. Although results show that patients could benefit from smoking cessation strategies centered on smoking's fetal/neonatal health risks, organizational interventions that focus on changing staff attitudes about patient desire to quit smoking may first need to be implemented. Chisolm MS, Brigham EP, Lookatch SJ, Tuten M, Strain EC, Jones HE. Cigarette smoking knowledge, attitudes, and practices of patients and staff at a perinatal substance abuse treatment center. *J Subst Abuse Treat.* 2010 Oct; 39(3): 298-305.

Alcohol Use and Initial Smoking Lapses Among Heavy Drinkers in Smoking Cessation Treatment

Dr. Kahler and colleagues at Brown University conducted this study to examine alcohol use and its association with initial smoking lapses among heavy nondependent drinkers in smoking cessation treatment. Participants were 236 heavy drinking smokers in a randomized clinical trial testing the efficacy of incorporating brief alcohol intervention into smoking cessation treatment. Of the 178 participants who reported a smoking lapse, 41.5% lapsed when drinking alcohol. Those who had alcohol-involved lapses had significantly lower tobacco dependence severity and drank more drinks per week than those who had non-alcohol-involved lapses. The majority of alcohol-involved lapses were in a bar/restaurant, with other people, and when they were in a happy/good mood. In survival analyses with alcohol consumption as a time-varying covariate, moderate drinking days were associated with almost four times greater risk of smoking lapse than non-drinking days, and heavy drinking doubled the risk of lapsing compared with moderate drinking. Results suggest that alcohol-related lapses are qualitatively different from lapses that do not involve alcohol. Furthermore, among heavy drinkers in cessation treatment, even moderate alcohol use is associated with increased risk of smoking, with heavy drinking further increasing the risk. Smoking cessation treatments for heavy alcohol drinkers should highlight the lapse risk associated with any alcohol consumption and with heavy drinking during a quit smoking attempt. Kahler CW, Spillane NS, Metrik J. Alcohol use and initial smoking lapses among heavy drinkers in smoking cessation treatment. *Nicotine Tob Res.* 2010 Jul; 12(7): 781-785.

Single versus Recurrent Depression History: Differentiating Risk Factors Among Current US Smokers

Data from 1560 smokers aged 18 and older completing the National Comorbidity Survey - Replication (NCS-R) were examined to determine the relationship between the chronicity of Major Depressive Disorder (MDD), smoking characteristics, cessation history, nicotine dependence, comorbidity with psychiatric disorders, and current functional impairments. Lifetime history of MDD was categorized according to chronicity: No history (No MDD), single episode (MDD-S) and recurrent depression (MDD-R). The results indicated that MDD-R smokers reported fewer lifetime cessation efforts, smoked more cigarettes, had higher levels of nicotine dependence, had higher rates of comorbid psychiatric disorders and greater functional impairment than smokers with No MDD. MDD-S smokers were not consistently distinguished from No MDD smokers on cessation attempts, level of daily smoking, nicotine dependence or functional impairment indices. The study highlights the importance of chronicity when characterizing depression-related risk of persistent smoking behavior. Although clinical trials suggest MDD-R smokers specifically benefit from specialized behavioral treatments, these services are not widely available and more efforts are needed to engage MDD-R smokers in efficacious treatments. Strong DR, Cameron A, Feuer S, Cohn A, Abrantes AM, Brown RA. Single versus recurrent depression history: differentiating risk

factors among current US smokers. *Drug Alcohol Depend.* 2010 Jun 1; 109(1-3): 90-95.

Do Faxed Quitline Referrals Add Value to Dental Office-Based Tobacco-Use Cessation Interventions?

Dr. Gordon and colleagues from the Oregon Research Institute sought to compare the effectiveness of a dental practitioner advice and brief counseling intervention to quit tobacco use versus usual care for patients in community health centers on tobacco cessation, reduction in tobacco use, number of quit attempts, and change in readiness to quit. Fourteen federally funded community health center dental clinics that serve diverse racial/ethnic groups in 3 states (Mississippi, New York, and Oregon) were randomized to the intervention (brief advice and assistance, including nicotine replacement therapy) or usual care group. The investigators enrolled 2549 smokers. Participants in the intervention group reported significantly higher abstinence rates at the 7.5-month follow-up, for both point prevalence ($F(1,12) = 6.84$; $P < .05$) and prolonged abstinence ($F(1,12) = 14.62$; $P < .01$) than did those in the usual care group. The results of the study suggest the viability and effectiveness of tobacco cessation services delivered to low-income smokers via their dental health care practitioner in community health centers. Tobacco cessation services delivered in public dental clinics have the potential to improve the health and well-being of millions of Americans. Gordon JS, Andrews JA, Crews KM, Payne TJ, Severson HH, Lichtenstein E. Do faxed quitline referrals add value to dental office-based tobacco-use cessation interventions? *J Am Dent Assoc.* 2010 Aug; 141(8): 1000-1007.

Breath Carbon Monoxide Output is Affected by Speed of Emptying the Lungs

Researchers have used breath carbon monoxide (CO) cutoff values ranging from 4 to 10 ppm to define abstinence in cigarette-smoking cessation research and reductions in CO as a measure of acute abstinence in laboratory research. The current study used a reversal design to investigate effects of exhalation speed on CO output in four groups (non-, light, moderate, and heavy smokers; $n = 20$ per group). In one condition, participants were instructed to empty their lungs as quickly as possible (fast), whereas in a different condition, participants were instructed to empty their lungs at a slow pace (slow). Conditions were counterbalanced and repeated twice for each participant. The results indicated that for all groups, speed of exhalation was significantly lower during the slow condition than during the fast condition, and CO output was significantly higher during the slow condition than during the fast condition. Sensitivity and specificity analyses revealed that the optimal CO cutoff for smoking abstinence was 3 ppm during the fast condition versus 4 ppm during the slow condition. Additionally, when heavy smokers switched from exhaling slow to exhaling fast, they showed an approximately 30% reduction in CO. The results suggest that exhalation speed should be monitored when CO is used as a measure of smoking status for laboratory and smoking cessation research. If exhalation speed is not monitored when using CO to verify smoking cessation, more conservative CO cutoff values should be used to avoid false negative CO readings. Raiff BR, Faix C, Turturici M, Dallery J. Breath carbon monoxide output is affected by speed of emptying the lungs: implications for laboratory and smoking cessation research. *Nicotine Tob Res.* 2010 Aug; 12(8): 834-838.

Negative Affect as a Mediator of the Relationship between Vigorous-Intensity Exercise and Smoking

The present cross-sectional study evaluated whether people who engage in vigorous-intensity exercise are better able to regulate negative affective states,

thereby changing core maintenance factors of smoking. Participants were a community sample of adults (n = 270) who completed self-report measures of physical activity, cigarette smoking, anxiety sensitivity, and negative affect. Vigorous-intensity exercise was related to lower levels of cigarette smoking, accounting for 10% of the variance in smoking. Additionally, negative affect mediated the relationship between vigorous-intensity physical activity and cigarette smoking, accounting for about 12% of this relation. Furthermore, these relationships were stronger for individuals with high anxiety sensitivity than for those with low anxiety sensitivity; including anxiety sensitivity as a moderator of the mediated relationship increased the amount of variance accounted for by negative affect to 17%. The findings are discussed in relation to developing further scientific insight into the mechanisms and pathways relevant to understanding the association among vigorous-intensity exercise, smoking, and emotional vulnerability. Tart CD, Leyro TM, Richter A, Zvolensky MJ, Rosenfield D, Smits JA. Negative affect as a mediator of the relationship between vigorous-intensity exercise and smoking. *Addict Behav.* 2010 Jun; 35(6): 580-585.

A Pilot Study of Aerobic Exercise as an Adjunctive Treatment for Drug Dependence

Intervention to increase exercise in drug dependent patients represents a potentially useful yet unexplored strategy for preventing relapse. Researchers from Brown University conducted this pilot study to examine the aerobic exercise as an adjunct to substance abuse treatment among drug dependent patients. Participants included 16 (31% female, 38.3 years old) drug dependent patients who participated in a 12-week, moderate-intensity aerobic exercise intervention. Participants attended a mean of 8.6 sessions (out of 12). Participants demonstrated a significant increase in percent days abstinent for both alcohol and drugs at the end of treatment, and those who attended at least 75% of the exercise sessions had significantly better substance use outcomes than those who did not. In addition, participants showed a significant increase in their cardiorespiratory fitness by the end of treatment. While preliminary, this study is one of the first to demonstrate the feasibility of incorporating aerobic exercise during drug abuse treatment. Future randomized control trials are a necessary next step to test the efficacy of a moderate-intensity aerobic exercise intervention as an adjunct to drug abuse treatment. Brown RA, Abrantes AM, Read JP, Marcus BH, Jakicic J, Strong DR, Oakley JR, Ramsey SE, Kahler CW, Stuart GG, Dubreuil ME, Gordon AA. A pilot study of aerobic exercise as an adjunctive treatment for drug dependence. *Ment Health Phys Act.* 2010 Jun 1; 3(1): 27-34.

Practicing Self-Control Lowers the Risk of Smoking Lapse

Recent research has suggested that practicing small acts of self-control can lead to an improvement in self-control performance. Because smoking cessation requires self-control, it was hypothesized that a treatment that builds self-control should help in quitting smoking. A total of 122 smokers either practiced small acts of self-control for 2 weeks before quitting smoking or practiced a task that increased their awareness of self-control or feelings of confidence, without exercising self-control. Smoking status was assessed using daily telephone calls and was biochemically verified. Individuals who practiced self-control remained abstinent longer than those who practiced tasks that did not require self-control. Supplemental analyses suggested that the increased abstinence was a product of building self-control strength and were not produced by changes in feelings that practicing should help in cessation, effort exerted on the practice task, or thinking more about self-control while practicing. Muraven M. Practicing self-control lowers the risk of smoking lapse. *Psychol Addict Behav.* 2010 Sep; 24(3): 446-452.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Research on Pharmacotherapies for Drug Abuse

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Methadone is the current recommended treatment for opioid dependence during pregnancy; however, prenatal exposure to methadone is associated with neonatal abstinence syndrome (NAS) which requires medication and extended hospitalization. Buprenorphine, a partial mu-opioid agonist, is an alternative treatment for opioid dependence, but has not been studied extensively in pregnancy. This study compared the efficacy of methadone to buprenorphine in 175 pregnant women with opioid dependence at 8 sites. Primary outcomes were the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of hospital stay for neonates, and neonatal head circumference. Treatment was discontinued by 16 of the 89 women in the methadone group (18%) and 28 of the 86 women in the buprenorphine group (33%). A comparison of the 131 neonates whose mothers were followed to the end of pregnancy according to treatment group (58 exposed to buprenorphine and 73 exposed to methadone) showed that the buprenorphine group required significantly less morphine (mean dose 1.1 mg vs 10.4 mg, $P < 0.0091$), had a significantly shorter hospital stay (10.0 days vs 17.5 days, $P < 0.0091$) and had a significantly shorter duration of treatment for NAS (4.1 days vs 9.9 days, $P < 0.003125$). There were no other significant differences between groups in other primary or secondary outcomes or in the rates of maternal or neonatal adverse events. The results are consistent with the use of buprenorphine as an acceptable treatment for opioid dependence in pregnant women. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine*. 2010 363: 2320-2331.

Revised Dose Schema of Sublingual Buprenorphine in the Treatment of the Neonatal Opioid Abstinence Syndrome

A randomized, Phase I, open-label active control clinical trial comparing sublingual buprenorphine to oral morphine in 24 term infants requiring pharmacological treatment for neonatal abstinence syndrome (NAS) was carried out in a large, urban, tertiary care hospital. Outcomes were neonatal safety, length of treatment, and length of hospitalization. Sublingual buprenorphine was found to be safe and effective in this study. Infants treated with buprenorphine had a 23-day length of treatment compared to 38 days for those treated with morphine ($p = 0.01$), representing a 40% reduction. Length of hospital stay in the buprenorphine group was reduced 24%, from 42 to 32 days ($p = 0.05$). The conclusions were that sublingual buprenorphine was safe in

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NAS, with a substantial efficacy advantage over standard of care therapy with oral morphine. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction*. 2010 Oct. 6 (Epub ahead of print).

Fetal Neurobehavioral Effects of Exposure to Methadone or Buprenorphine

As part of a double-blind study of medication treatment for opioid dependence during pregnancy, 17 opioid-dependent pregnant women maintained on either buprenorphine or methadone underwent fetal monitoring at 24, 28, 32, and 36 weeks gestation. Maternal demographic information and infant outcomes did not significantly differ by medication group. Earlier in gestation (24 and 28 weeks), buprenorphine-exposed fetuses had higher levels of fetal heart rate variability, more accelerations in fetal heart rate and greater coupling between fetal heart rate and fetal movement than the methadone-exposed group (all $ps < .05$). Later in gestation (32 and 36 weeks), buprenorphine-exposed fetuses displayed less suppression of motor activity and longer duration of movements than the methadone-exposed group (all $ps < .05$). These results may have implications for the optimal treatment of the opioid-dependent pregnant woman. Jansson LM, DiPietro JA, Velez M, Elko A, Williams E, Milio L, O'Grady K, Jones HE. Fetal neurobehavioral effects of exposure to Methadone or Buprenorphine. *Neurotoxicology and Teratology*. 2010 Sept 22 (Epub ahead of print).

Acute Effects of Intramuscular and Sublingual Buprenorphine and Buprenorphine/Naloxone in Non-dependent Opioid Abusers

A sublingual combination formulation was developed containing buprenorphine and naloxone with the intent of decreasing abuse liability in opioid-dependent individuals. However, the addition of naloxone may not limit abuse potential of this medication when taken by individuals without opioid physical dependence. The present study investigated the effects of buprenorphine alone and in combination with naloxone administered intramuscularly and sublingually to non-dependent opioid abusers. In a within-subject crossover design, non-dependent opioid-experienced volunteers ($N = 8$) were administered acute doses of buprenorphine (4, 8, and 16 mg) and buprenorphine/naloxone (4/1, 8/2, and 16/4 mg) via both intramuscular and sublingual routes, intramuscular hydromorphone (2 and 4 mg as an opioid agonist control), and placebo, for a total of 15 drug conditions. Laboratory sessions were conducted twice per week using a double-blind, double-dummy design. Buprenorphine and buprenorphine/naloxone engendered effects similar to hydromorphone. Intramuscular administration produced a greater magnitude of effects compared to the sublingual route at the intermediate dose of buprenorphine and at both the low and high doses of the buprenorphine/naloxone combination. The addition of naloxone did not significantly alter the effects of buprenorphine. These results suggest that buprenorphine and buprenorphine/naloxone have similar abuse potential in non-dependent opioid abusers, and that the addition of naloxone at these doses and in this dose ratio confers no evident advantage for decreasing the abuse potential of intramuscular or sublingual buprenorphine in this population. Duke AN, Correia CJ, Walsh SL, Bigelow GE, Strain EC. Acute effects of intramuscular and sublingual Buprenorphine and Buprenorphine/naloxone in non-dependent opioid abusers. *Psychopharmacology*. 2010 Aug; 211(3): 303-312.

Use of Naltrexone to Treat Opioid Addiction in a Country in which Methadone and Buprenorphine Are Not Available

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Opioid dependence is one of the most severe drug dependencies. Naltrexone is a medication that completely blocks the subjective and other effects of opioids and, when administered to detoxified opioid addicts and taken as directed, prevents relapse and helps maintain abstinence. The major problem with naltrexone is poor compliance, particularly in countries in which there is a treatment alternative based on substitution of illicit opioids such as heroin with orally administered opioid agonists (methadone) or partial agonist/antagonists (buprenorphine). In Russia, substitution therapy is forbidden by law, and naltrexone is the only available pharmacotherapy for heroin dependence. Due to the lack of alternatives to naltrexone and stronger family control of compliance (adherence), naltrexone is more effective for relapse prevention and abstinence stabilization in Russia than in Western countries. Long-acting, sustained-release formulations (injectable and implantable) seem particularly effective compared with oral formulations. This article summarizes the results of studies conducted in Russia during the past 10 years that demonstrate these points. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep.* 2010 Oct; 12(5): 448-453.

Long-acting Injectable Versus Oral Naltrexone Maintenance Therapy with Psychosocial Intervention for Heroin Dependence: A Quasi-experiment

To conduct a quasi-experimental comparison of early clinical outcomes between injectable, sustained-release, depot naltrexone formulation versus oral naltrexone maintenance therapy in individuals with opiate dependence. Early retention in treatment and urine-confirmed opiate use in the first 8 weeks post-detoxification were compared between patients (diagnosed as opiate-dependent according to DSM-IV criteria) participating in two concurrently run randomized clinical trials of oral (n = 69; patients treated from September 1999 to May 2002) and long-acting injectable (n = 42; patients treated from November 2000 to June 2003) naltrexone maintenance therapy with psychosocial therapy. Long-acting injectable naltrexone produced significantly better outcome than oral naltrexone on days retained in treatment ($F(1,106) = 6.49, P = .012$) and for 1 measure of opiate use ($F(1,106) = 5.26, P = .024$); other measures were not significantly different, but differences were in the same direction. In sub-analyses, there were interaction effects between baseline heroin use severity and type of treatment. In sub-analyses, heroin users with more severe baseline use showed better retention with oral naltrexone maintenance therapy combined with intensive psychotherapy (behavioral naltrexone therapy) as compared to retention shown by severe heroin users treated with long-acting naltrexone injections combined with standard cognitive-behavioral therapy ($\chi^2(1) = 9.31, P = .002$); less severe heroin users evidenced better outcomes when treated with long-acting injectable naltrexone. This quasi-experimental analysis provides tentative indications of superior outcomes for heroin-dependent patients treated with long-acting injectable naltrexone compared to oral naltrexone. The finding that heroin users with more severe baseline use achieved better outcomes with oral naltrexone is most probably attributable to the intensive nature of the psychosocial treatments provided and points to the opportunity for continued research in augmenting injectable naltrexone with psychosocial strategies to further improve outcome, especially in individuals with more severe use. The results should be considered exploratory given the quasi-experimental nature of the study. Brooks AC, Comer SD, Sullivan MA, Bisaga A, Carpenter KM, Raby WM, Yu E, O'Brien CP, Nunes EV. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. *J Clin Psychiatry.* 2010 Oct; 71(10):1371-8. Epub 2010 Jul 13.

Effects of Repeated Tramadol and Morphine Administration on

Psychomotor and Cognitive Performance in Opioid-dependent Volunteers

Tramadol is an atypical, mixed mechanism analgesic used to treat moderate to severe pain. Based on evidence that tramadol has relatively low abuse potential and can relieve opioid withdrawal, tramadol may be useful for treating opioid dependence. The purpose of this study was to assess the performance side-effect profile of tramadol. Nine opioid-dependent volunteers completed a performance battery following 5-7 days of subcutaneous morphine (15 mg, 4 times/day) and two doses of oral tramadol (50, 200 mg, 4 times/day) in a within subject cross-over design. Morphine was always the first condition, and the order of the two tramadol doses was randomized and double blind. Performance was significantly worse in the morphine condition relative to one or both tramadol doses on measures of psychomotor speed/coordination (circular lights task), psychomotor speed/pattern recognition (DSST speed measure) and psychomotor speed/set shifting (trail-making tasks). There were no significant differences among conditions in DSST accuracy, simple reaction time, divided attention, working memory, episodic memory, metamemory, or time estimation. Neither tramadol dose was associated with worse performance than morphine on any measure. Although practice sessions were conducted prior to the first session to reduce order effects, the possibility that residual practice effects contributed to the differences between tramadol and morphine cannot be ruled out. The high tramadol dose produced worse performance than the low dose only on the balance measure. These findings suggest that tramadol is generally a safe medication with respect to cognitive and psychomotor measures and support tramadol's further evaluation as an opioid-dependence treatment. Mintzer MZ, Lanier RK, Lofwall MR, Bigelow GE, Strain EC. Effects of repeated tramadol and morphine administration on psychomotor and cognitive performance in opioid-dependent volunteers. *Drug Alcohol Depend.* 2010 Oct 1; 111(3): 265-268. Epub 2010 Jun 9.

Physical Dependence Potential of Daily Tramadol Dosing in Humans

Tramadol is an atypical, mixed-mechanism analgesic involving both opioid and catecholamine processes that appears to have low abuse potential and may be useful as a treatment for opioid dependence. The current study assessed the level of physical dependence and opioid blockade efficacy produced by daily maintenance on oral tramadol. Nine residential opioid-dependent adults were maintained on two doses of daily oral tramadol (200 and 800 mg) for approximately 4-week intervals in a randomized, double-blind, crossover design. The acute effects of intramuscular placebo, naloxone (0.25, 0.5, and 1.0 mg), and hydromorphone (1.5, 3.0, and 6.0 mg) were tested under double-blind, randomized conditions. Outcomes included observer- and subject-rated measures and physiologic indices. Challenge doses of naloxone resulted in significantly higher mean peak withdrawal scores compared to placebo. Withdrawal intensity from naloxone was generally greater during 800 versus 200 mg/day tramadol maintenance. Mean peak ratings of agonist effects were elevated at higher hydromorphone challenge doses, but did not differ significantly between tramadol doses. Physiologic measures were generally affected by challenge conditions in a dose-dependent manner, with few differences between tramadol maintenance dose conditions. Chronic tramadol administration produces dose-related opioid physical dependence, without producing dose-related attenuation of agonist challenge effects. Tramadol may be a useful treatment for patients with low levels of opioid dependence or as a treatment for withdrawal during opioid detoxification, but does not appear to be effective as a maintenance medication due to a lack of opioid cross-tolerance. Lanier RK, Lofwall MR, Mintzer MZ, Bigelow GE, Strain EC. Physical dependence potential of daily tramadol dosing in humans. *Psychopharmacology (Berl).* 2010 Sep; 211(4): 457-466. Epub 2010 Jun 30.

Intravenous Oxycodone, Hydrocodone, and Morphine in Recreational Opioid Users: Abuse Potential and Relative Potencies

Nonmedical use and abuse of prescription opioids is an increasing public health problem. Intravenous (IV) administration of opioid analgesics intended for oral use is not uncommon; yet, little is known about the relative abuse potential of these drugs when administered intravenously to recreational opioid abusers without physical dependence. This inpatient study employed a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential of IV doses of oxycodone, hydrocodone, and morphine. Nine healthy adult participants reporting recreational opioid use and histories of IV opioid use completed 11 experimental sessions, including one active-dose practice session. IV doses were infused over 5 min and included three identical doses of each opioid (5, 10, and 20 mg/10 ml) and saline placebo.

Physiological, subjective, and performance effects were collected before and for 6 h after drug administration. All three opioids produced prototypical mu agonist effects (e.g., miosis; increased ratings of liking) that were generally dose-related. Pharmacodynamic effects were observed within 5 min of IV administration. Physiological effects were more prolonged than subjective effects for all three drugs. While the magnitude of effects was generally comparable across drugs and qualitatively similar, valid potency assays indicated the following potency relationship: oxycodone > morphine > hydrocodone. There were modest potency differences between oxycodone, hydrocodone, and morphine, but their overall profile of effects was similar, indicating significant abuse potential when administered intravenously. Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. *Psychopharmacology (Berl)*. 2010 Oct; 212(2): 193-203. Epub 2010 Jul 28.

Randomized, Double-blind, Placebo-controlled Trial of Disulfiram for the Treatment of Cocaine Dependence in Methadone-stabilized Patients

This study examined the dose-related efficacy of disulfiram for treating cocaine dependence in methadone-stabilized cocaine dependent participants. One hundred and sixty-one cocaine- and opioid-dependent volunteers were entered into a 14-week, double blind, randomized, placebo-controlled clinical trial at two sites. Participants were stabilized on methadone during weeks 1-2 and received disulfiram at 0, 62.5, 125 or 250mg/day during weeks 3-14. All participants also received weekly cognitive behavioral therapy. Thrice-weekly urine samples and weekly self-reported drug use assessments were obtained. Baseline subject characteristics, retention and drug use did not differ across groups. Outcome analyses were performed on those who participated beyond week 2. Opioid-positive urine samples and self-reported opioid use did not differ by treatment group. The prevalence of alcohol use was low prior to and during the trial and did not differ by treatment group. Cocaine-positive urines increased over time in the 62.5 and 125mg disulfiram groups and decreased over time in the 250mg disulfiram and placebo groups ($p < 0.0001$). Self-reported cocaine use increased in the 125mg disulfiram group relative to the other three treatment groups ($p = 0.04$). Disulfiram may be contraindicated for cocaine dependence at doses < 250 mg/day. Whether disulfiram at higher doses is efficacious in reducing cocaine use in dually cocaine and opioid dependent individuals needs to be determined. Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, Gonsai K, Cargile C, Sofuoglu M, Chopra MP, Gonzalez-Haddad G, Carroll KM, Kosten TR. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug Alcohol Depend*. 2010 Sep 7. [Epub ahead of print]

A Double-Blind, Placebo-Controlled Pilot Trial of Acamprosate for the Treatment of Cocaine Dependence

Although the exact mechanism of action of acamprosate is unknown, evidence suggests that it decreases excitatory amino acid activity by post-synaptic inhibition of the NMDA subtype of glutamate receptors, it has been shown to be effective for the treatment of alcohol dependence. It is possible that the activity of acamprosate via modulating glutamatergic activity could also reduce craving for cocaine and impact abstinence in cocaine dependence. A double-blind placebo-controlled pilot trial of acamprosate was carried out to determine if it could be a possible treatment for cocaine dependence. Sixty male and female cocaine dependent patients were included in a nine week double-blind, placebo-controlled trial. After a one-week baseline, patients were randomized to receive acamprosate 666 mg three times daily or identical placebo tablets for eight weeks. The primary outcome measure was cocaine use as determined by twice weekly urine drug screens. Thirty-six patients (60%) completed the trial, with no significant between-group difference in treatment retention. Percent cocaine positive urine drug screens did not differ between the two groups. Acamprosate was no better than placebo in reducing cocaine craving, reducing cocaine withdrawal symptoms, or improving measures of drug use severity from the Addiction Severity Index. Adverse events in this trial were generally mild and were evenly distributed between the two groups. The study conclusions were that acamprosate was well tolerated but was no more efficacious than placebo in promoting abstinence from cocaine in cocaine dependent patients. Acamprosate does not appear to be a promising medication for the treatment of cocaine dependence. Kampman KM, Dackis C, Pettinati HM, Lynch KG, Sparkman T, O'Brien CP. A double-blind, placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence *Addictive Behaviors* 2010 Nov. 10 (Epub ahead of print).

A Placebo-controlled Trial of Memantine for Cocaine Dependence with High-value Voucher Incentives During a Pre-randomization Lead-in Period

Preclinical findings suggest that the inhibition of NMDA glutamatergic neurotransmission may have beneficial effects in the treatment of cocaine dependence. The hypothesis that memantine, a low potency, uncompetitive NMDA receptor antagonist, would be safe and effective in the treatment of cocaine dependence, particularly in preventing relapse to cocaine use in abstinent individuals was tested in a clinical trial in cocaine dependent patients with a targeted N of 112. The trial began with a 2-week placebo lead-in period during which patients received high-value voucher contingency management to induce abstinence. Participants were then randomized to receive either memantine 20 mg bid (N = 39) or placebo (N = 42) for 12-weeks in combination with individual relapse-prevention therapy. The randomization was stratified by abstinence status during the lead-in period. The primary outcome was the weekly proportion of days of cocaine use. There were no significant differences in cocaine use outcome between the groups treated with memantine versus placebo. Thus, the efficacy of memantine 40 mg/d for the treatment of cocaine dependence was not supported. Urine-confirmed abstinence during the lead-in period was achieved by 44% of participants, and was a strong predictor of subsequent cocaine abstinence during the trial. This suggests that this clinical trial design, an intensive behavioral intervention during a lead-in period, resolves cocaine dependent patients into two subgroups, one that rapidly achieves sustained abstinence and may not need a medication, and another that displays persistent cocaine use and would most likely benefit from a medication to help induce abstinence. Targeting the latter subgroup may advance medication development efforts. Bisaga A, Aharonovich E, Cheng WY, Levin FR, Mariani JJ, Raby WN, Nunes EV. A placebo-controlled

trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. *Drug and Alcohol Dep.* 2010 111: 97-104.

Prenatal Cocaine Exposure, Gender, and Adolescent Stress Response: a Prospective Longitudinal Study

Prenatal cocaine exposure is associated with alterations in arousal regulation in response to stress in young children. However, relations between cocaine exposure and stress response in adolescence have not been examined. The authors examined salivary cortisol, self-reported emotion, heart rate, and blood pressure (BP) responses to the Trier Social Stress Test (TSST) in 49 prenatally cocaine and other drug exposed (PCE) and 33 non-cocaine-exposed (NCE) adolescents. PCE adolescents had higher cortisol levels before and after stress exposure than NCE adolescents. PCE girls showed an elevated anxiety response to stress (compared to NCE girls) and PCE boys showed a dampened diastolic BP response (compared to NCE boys). Girls showed higher anger response and lower pre-stress systolic BP than boys. Group differences were found controlling for potential confounding variables and were not moderated by caregiver-child relationship quality (although relationship quality predicted HPA axis and anxiety response). The findings suggest that prenatal drug exposure is associated with altered stress response in adolescence and that gender moderates this association. Chaplin TM, Freiburger MB, Mayes LC, Sinha R. Prenatal cocaine exposure, gender, and adolescent stress response: a prospective longitudinal study. *Neurotoxicol Teratol.* 2010 Nov-Dec; 32(6):595-604. Epub 2010 Sep 17.

Discriminative Stimulus, Subject-rated and Cardiovascular Effects of Cocaine Alone and in Combination with Aripiprazole in Human

Aripiprazole is a dopamine D(2) receptor partial agonist undergoing evaluation as a pharmacotherapy for stimulant-use disorders. Acutely administered aripiprazole attenuates the discriminative stimulus and other behavioral effects of d-amphetamine in humans; however, whether aripiprazole attenuates the effects of more commonly abused stimulants is unknown. The aim of this experiment was to assess the discriminative stimulus, subject-rated and cardiovascular effects of oral cocaine alone and following acute administration of aripiprazole in humans. Eight cocaine-dependent subjects learned to discriminate 150 mg cocaine from placebo. After acquiring the discrimination, the effects of cocaine (0, 25, 50, 100 and 200 mg) administered alone and in combination with aripiprazole (15 mg) were determined. Significant effects of cocaine were observed for the drug discrimination task, stimulant-like subject-rated effects and heart rate. Limited effects of aripiprazole were revealed. However, for most measures, fewer doses of cocaine were significantly greater than placebo when combined with aripiprazole, suggesting a reduction in the discriminative stimulus, self-reported and cardiovascular effects of cocaine. These data are consistent with previous studies that have tested acutely administered aripiprazole in combination with d-amphetamine and suggest that the ability of aripiprazole to modify stimulant effects is a function of the duration of treatment (acute vs. chronic). Lile JA, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative stimulus, subject-rated and cardiovascular effects of cocaine alone and in combination with aripiprazole in humans. *J Psychopharmacol.* 2010 Oct 15. [Epub ahead of print].

Reinforcing Effects of d-Amphetamine: Influence of Novel Ratios on a Progressive-Ratio Schedule

Progressive-ratio schedules are useful for studying the reinforcing effects of drugs. Earlier human laboratory studies showed that d-amphetamine

significantly increased break points relative to placebo. However, the magnitude of the increase was modest, which may be attributable to rather high levels of placebo responding. The authors used novel response requirements in a modified progressive-ratio procedure and hypothesized that the altered range of response requirements would decrease responding for placebo and increase responding for d-amphetamine. Eight participants completed the study. The participants first sampled oral doses of d-amphetamine (0, 8, 16, and 24 mg). In subsequent sessions, the participants were offered the opportunity to work for the sampled dose on a modified progressive-ratio procedure with response requirements ranging from 400 to 1800 mouse clicks. A battery of participant-rated drug-effect questionnaires, a performance measure, and cardiovascular measures were included to more fully characterize the effects of d-amphetamine. Placebo maintained low levels of responding. The intermediate dose of d-amphetamine increased responding significantly above placebo levels. d-Amphetamine produced prototypical subject-rated effects that were an orderly function of dose. These data suggest that the modified response requirements resulted in lower levels of placebo taking and a larger separation between the number of placebo and d-amphetamine capsules earned. Sevak RJ, Stoops WW, Glaser PE, Hays LR, Rush CR. Reinforcing effects of d-amphetamine: influence of novel ratios on a progressive-ratio schedule. *Behav Pharmacol*. 2010 Oct 12. [Epub ahead of print].

Subjective and Physiological Effects of Acute Intranasal Methamphetamine during d-Amphetamine Maintenance

Methamphetamine abuse and dependence are significant public-health concerns. Behavioral therapies are effective for reducing methamphetamine use. However, many patients enrolled in behavioral therapies are unable to achieve significant periods of abstinence, suggesting other strategies like pharmacotherapy are needed. This experiment determined the subjective and physiological effects of intranasal methamphetamine during D-amphetamine maintenance in eight non-treatment-seeking stimulant-dependent participants. The authors predicted D-amphetamine maintenance would attenuate the acute subjective effects of intranasal methamphetamine. The authors also predicted intranasal methamphetamine would be well tolerated during D-amphetamine maintenance. After at least 7 days of maintenance on sustained-release D-amphetamine (0 and 45 mg/day), participants were administered ascending doses of intranasal methamphetamine (0, 2.5, 5, 10, and 20 mg) across two experimental sessions. Intranasal methamphetamine doses were separated by 90 min. Intranasal methamphetamine produced prototypical subjective and physiological effects (e.g., increased ratings of Like Drug; increased heart rate, blood pressure, and body temperature). The acute effects of intranasal methamphetamine were significantly diminished during D-amphetamine maintenance relative to placebo maintenance. These results are concordant with those of clinical trials and provide further support for the use of agonist replacement therapy to manage methamphetamine dependence. Additional research in humans is needed to determine the effectiveness of D-amphetamine under different experimental conditions that more closely reflect use in the natural environment (e.g., higher methamphetamine doses) and behavioral arrangements that are predictive of pharmacotherapy effectiveness (e.g., drug self-administration). Rush CR, Stoops WW, Lile JA, Glaser PE, Hays LR. Subjective and physiological effects of acute intranasal methamphetamine during d-amphetamine maintenance. *Psychopharmacology (Berl)*. 2010 Nov 12. [Epub ahead of print].

Minocycline Attenuates Subjective Rewarding Effects of Dextroamphetamine in Humans

Minocycline, a tetracycline antibiotic, interacts with brain glutamate and

dopamine neurotransmission. In preclinical studies, minocycline attenuated amphetamine-induced acute dopamine release and subsequent behavioral sensitization. The goal of this study was to determine minocycline's effects on the acute physiological, behavioral, and subjective responses to dextroamphetamine (DAMP) in healthy volunteers. Ten healthy volunteers participated in an outpatient double-blind, placebo-controlled, crossover study. Subjects had a 5-day treatment period with either minocycline (200 mg/day) or placebo and then were crossed over for 5 days of the other treatment. After 2 days of taking the study medication, on days 3 and 4, subjects were randomly assigned to double-blind acute challenge with either 20 mg/70 kg DAMP or placebo DAMP (randomly labeled as drug A or B) and then crossed over to the other challenge. On day 5 (experimental session 3), subjects had the opportunity to self-administer either placebo or DAMP capsules by working on a progressive ratio computer task. Minocycline attenuated DAMP-induced subjective rewarding effects but did not change DAMP choice behavior. Minocycline treatment speeded reaction times on a Go No-Go task and reduced plasma cortisol levels. Conclusion: These findings warrant further studies examining the potential use of minocycline for stimulant addiction. Sofuoglu M, Mooney M, Kosten T, Waters A, Hashimoto K. Minocycline attenuates subjective rewarding effects of dextroamphetamine in humans. *Psychopharmacology (Berl)*. 2010 Sep 14 [Epub ahead of print].

The Effects of Progesterone Pretreatment on the Response to Oral d-Amphetamine in Women

Stimulant abuse continues to be a problem, particularly for women. There is increasing preclinical and clinical evidence showing that the hormone progesterone attenuates the behavioral effects of cocaine, and this effect is primarily observed in females. The purpose of the present study was to determine if progesterone would also alter the behavioral effects of another stimulant, oral d-amphetamine (AMPH) in women. Eighteen normal non-drug abusing women completed eight outpatient sessions over two menstrual cycles. During the follicular phase of each cycle, women were administered AMPH (0, 10, 20 mg); in one cycle they were pretreated with oral micronized progesterone (200 mg) and in another cycle they were pretreated with placebo progesterone. Each session, participants completed a range of tasks including subjective measures of abuse liability, cognitive performance tasks, and behavioral measures of impulsivity and risk-taking. AMPH produced dose-related increases in positive subjective effects and these effects were enhanced by progesterone pretreatment. AMPH alone, or in combination with progesterone, had little effect on performance or behavioral measures of impulsivity. These results are in contrast with previous studies showing that progesterone attenuates the subjective response to cocaine and nicotine. Additional studies are needed to explore the modulatory role of progesterone on the effects of AMPH to determine whether progesterone has any clinical utility for AMPH abuse. Reed SC, Levin FR, Evans SM. The effects of progesterone pretreatment on the response to oral d-amphetamine in women. *Horm Behav*. 2010 Aug; 58(3): 533-543. Epub 2010 Apr 24.

During Pregnancy, Recreational Drug-using Women Stop Taking Ecstasy (3,4-methylenedioxy-N-methylamphetamine) and Reduce Alcohol Consumption, but Continue to Smoke Tobacco and Cannabis: Initial Findings from the Development and Infancy Study

While recreational drug use in UK women is prevalent, to date there is little prospective data on patterns of drug use in recreational drug-using women immediately before and during pregnancy. A total of 121 participants from a wide range of backgrounds were recruited to take part in the longitudinal

Development and Infancy Study (DAISY) study of prenatal drug use and outcomes. Eighty-six of the women were interviewed prospectively while pregnant and/or soon after their infant was born. Participants reported on use immediately before and during pregnancy and on use over their lifetime. Levels of lifetime drug use of the women recruited were high, with women reporting having used at least four different illegal drugs over their lifetime. Most users of cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA) and other stimulants stopped using these by the second trimester and levels of use were low. However, in pregnancy, 64% of the sample continued to use alcohol, 46% tobacco and 48% cannabis. While the level of alcohol use reduced substantially, average tobacco and cannabis levels tended to be sustained at pre-pregnancy levels even into the third trimester (50 cigarettes and/or 11 joints per week). In sum, while the use of 'party drugs' and alcohol seems to reduce, levels of tobacco and cannabis use are likely to be sustained throughout pregnancy. The data provide polydrug profiles that can form the basis for the development of more realistic animal models. Moore DG, Turner JD, Parrott AC, Goodwin JE, Fulton SE, Min MO, Fox HC, Braddick FM, Axelsson EL, Lynch S, Ribeiro H, Frostick CJ, Singer LT. During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: initial findings from the Development and Infancy Study. *J Psychopharmacol.* 2010 Sep; 24(9): 1403-1410. Epub 2009 Nov 25.

The Safety and Efficacy of Varenicline in Cocaine Using Smokers Maintained on Methadone: a Pilot Study

In this double-blind, placebo-controlled trial, the authors compared varenicline (2 mg) to placebo for treatment for cocaine and tobacco dependence in 31 methadone-maintained subjects. Subjects received weekly counseling during the 12-week study participation. Our results indicate that varenicline is safe to give to this subject population, as there were no adverse events related to medication during this study. Varenicline was no more effective than placebo for abstinence from cocaine. Treatment with varenicline was associated with a reduced number of cigarettes smoked per day, even though subjects received only a brief education for smoking cessation. The self-report reduction in smoking was corroborated by CO levels and the Fagerström Test of Nicotine Dependence. However, self-ratings of positive mood on the Positive Affect Negative Affect Schedule did significantly decrease in the varenicline group as compared to the placebo group, although this appears to be due to randomization differences related to lifetime depression diagnosis. These preliminary findings may point to potential therapeutic value of varenicline for smoking cessation in cocaine users maintained on methadone. Poling J, Rounsaville B, Gonsai K, Severino K, Sofuoglu M. The safety and efficacy of varenicline in cocaine using smokers maintained on methadone: a pilot study. *Am J Addict.* 2010 Sep; 19(5): 401-408.

Methylphenidate Increases Choice of Cigarettes Over Money

Stimulants increase cigarette smoking in the naturalistic environment and laboratory. The effects of methylphenidate on a 9-trial, discrete cigarette versus money (\$0.25) choice task were tested to elucidate the mechanisms underlying stimulant-induced increases in smoking. Eleven participants who reported smoking 10-20 cigarettes/day completed the study. Four doses of methylphenidate (0, 10, 20, and 40 mg) were administered across 5 experimental sessions, with placebo administered twice. One hour following medication administration and at 30-min intervals thereafter, participants chose between smoking a cigarette and receiving US\$0.25. The primary behavioral outcome measure was number of cigarette choices. Methylphenidate increased the number of cigarette choices over money. Puffs per session and carbon monoxide levels increased significantly and caloric intake decreased

significantly following methylphenidate administration relative to placebo. The results of this study suggest that methylphenidate increases the relative reinforcing efficacy of cigarette smoking. Stimulant use may thus be an important consideration for individuals attempting to quit smoking. Stoops WW, Poole MM, Vansickel AR, Hays KA, Glaser PE, Rush CR. Methylphenidate increases choice of cigarettes over money. *Nicotine Tob Res.* 2010 Nov 8 [Epub ahead of print].

Increased Self-efficacy to Quit and Perceived Control Over Withdrawal Symptoms Predict Smoking Cessation Following Nicotine Dependence Treatment

To examine changes in nicotine withdrawal, nicotine craving, self-efficacy to quit smoking, and perceived control over withdrawal symptoms as predictors of smoking cessation following behavioral counseling and nicotine replacement therapy in a sample of smokers. The data were ascertained from a randomized effectiveness trial comparing nicotine patch to nicotine lozenge. Predictors of smoking cessation were assessed at baseline and 5 weeks post-baseline, and 24-hour point prevalence abstinence, biochemically confirmed, was assessed at the end-of-treatment (week 15) and 6 months after a target quit date (week 27). 642 treatment-seeking smokers randomized to 12 weeks of nicotine patch or nicotine lozenge. Participants who showed a greater increase in self-efficacy to quit smoking (OR=1.09, 95% CI: 1.02-1.16, $p=.01$) and perceived control over withdrawal symptoms (OR=1.02, 95% CI: 1.00-1.04, $p=.05$) were significantly more likely to have quit smoking at week 15. Participants who showed a greater increase in self-efficacy to quit smoking (OR=1.04, 95% CI: 1.01-1.06, $p=.01$) were significantly more likely to have quit smoking at week 27. Changes in withdrawal symptoms and craving were not related to week 15 or week 27 abstinence rates. The results highlight two relatively under-studied potential psychological predictors of abstinence following treatment for nicotine dependence. Behavioral counseling interventions to promote smoking cessation should help smokers develop confidence in their ability to quit smoking and increase their sense of control over withdrawal symptoms to increase their chances for cessation. Schnoll RA, Martinez E, Tatum KL, Glass M, Bernath A, Ferris D, Reynolds P. Increased self-efficacy to quit and perceived control over withdrawal symptoms predict smoking cessation following nicotine dependence treatment. *Addict Behav.* 2011 Jan-Feb; 36(1-2): 144-147. Epub 2010 Sep 24.

Comparison of Available Treatments for Tobacco Addiction Cigarette smoking is a major public health problem that causes more than 5 million deaths annually worldwide. Cigarette smoking is especially common among individuals with psychiatric comorbidity, including individuals with primary psychiatric disorders and other addictions. Effective behavioral and pharmacologic treatments for smoking cessation are available. Behavioral treatments including brief (< 3 min) counseling by physicians are effective. Seven first-line pharmacologic treatments are currently available: five nicotine replacement therapies, bupropion, and varenicline. In addition, clonidine and nortriptyline are second-line treatments for smoking cessation. These treatments increase the chances of quitting smoking by two- to threefold, supporting their use in smokers who are motivated to quit. However, effective treatments for many subpopulations, including smokers with psychiatric comorbidities as well as adolescent, pregnant, or postpartum smokers, remain to be developed and represent an important challenge. Herman AI, Sofuoglu M. Comparison of available treatments for tobacco addiction. *Curr Psychiatry Rep.* 2010 Oct; 12(5): 433-440.

Quantification and Comparison of Marijuana Smoking Practices: Blunts, Joints, and Pipes

The quantification method for collecting self-reported marijuana use data is not standardized as it is for alcohol or cigarettes, which presents a methodologic

challenge for marijuana use disorder treatment studies. Serum and urine markers of marijuana use have a long half-life, limiting their utility as a clinical trial outcome measure. Structured calendar-based interview procedures can accurately measure the frequency of self-reported marijuana use, but are unable to reliably address issues such as quantity of use or potency. This study compared the quantity and assigned-dollar value among users of blunts, joints, and pipes enrolled in two clinical trials testing pharmacotherapies for marijuana dependence. The timeline follow-back method was modified to incorporate using a surrogate substance to represent marijuana to enable participants to estimate the amount and value used. Blunt users were mostly black and Hispanic, while users of joints and pipes were primarily white. Participants reported that they placed 50% more marijuana in blunts than in joints and placed more than twice the amount of marijuana in blunts than in pipes. These findings demonstrate the feasibility of using a surrogate weight estimation procedure to augment calendar-based methods of measuring self-reported marijuana use. Individual variability in use practices limits the utility of this method to estimating within-subject comparisons, rather than between subject comparisons. Mariani JJ, Brooks D, Haney M, Levin FR. Quantification and comparison of marijuana smoking practices: Blunts, joints, and pipes. *Drug Alcohol Depend.* 2010 Sep 20 [Epub ahead of print].

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Research on Medical Consequences of Drug Abuse and Co-Occurring Infections (HIV/AIDS, HCV)

Effect of Methamphetamine on Expression of HIV Coreceptors and CC-Chemokines by Dendritic Cells

The United States is currently experiencing an entangled epidemic of HIV infection and use of different drugs of abuse, especially of methamphetamine (Meth). Blood monocyte-derived dendritic cells (DC) are the first line of defense against HIV-1 infection, and are the initial target of HIV-1 infection in injection drug users. DC-SIGN present on dendritic cells is the first molecule that facilitates HIV-1 infection independent of CD4 or HIV coreceptors. The aim of this study was to evaluate whether Meth acts as a cofactor in the pathogenesis of HIV-1 infection. Monocyte derived DCs, obtained from normal subjects were cultured with and without Meth±HIV-1B, followed by analyzing the gene and protein expression by real-time quantitative polymerase chain reaction (RT-PCR) and fluorescence-activated cell-sorting analyses, respectively. Our results show that Meth significantly enhances HIV infection, and downregulates the gene expression of chemokines and costimulatory molecules with reciprocal upregulation of HIV coreceptors and DC-SIGN by dendritic cells. Better understanding of the role of Meth in HIV-1 disease susceptibility and the mechanism through which Meth mediates its effects on HIV-1 infection may help to devise novel therapeutic strategies against HIV-1 infection in Meth using HIV-1 infected population. Nair MP, Saiyed ZM. Effect of methamphetamine on expression of HIV coreceptors and CC-chemokines by dendritic cells. *Life Sci.* 2010 Oct 19 [Epub ahead of print].

Increased Plasmacytoid Dendritic Cell Maturation and Natural Killer Cell Activation in HIV-1 Exposed, Uninfected Intravenous Drug Users

Increased natural killer (NK) activation has been associated with resistance to HIV-1 infection in several cohorts of HIV-1 exposed, uninfected individuals. Inheritance of protective NK receptor alleles (KIR3DS1 and KIR3DL1) has also been observed in a subset of HIV-1 exposed, uninfected individuals. However, the exact mechanism contributing to NK activation in HIV-1 exposed, uninfected intravenous drug users (EU-IDU) remains to be elucidated. The authors investigated the role of both host genotype and pathogen-induced dendritic cell modulation of NK activation during high-risk activity in a cohort of 15 EU-IDU individuals and 15 control, uninfected donors from Philadelphia. The activation status of NK cells and dendritic cells was assessed by flow cytometry and utilized functional assays of NK-DC cross-talk to characterize the innate immune compartment in EU-IDU individuals. As previously reported, NK cell activation (CD69) and/or degranulation (CD107a) was significantly increased in EU-IDU individuals compared with control uninfected donors (P = 0.0056, n =

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13). Genotypic analysis indicated that the frequency of protective KIR (KIR3DS1) and HLA-Bw4*80I ligands was not enriched in our cohort of EU-IDU individuals. Rather, plasmacytoid dendritic cells (PDC) from EU-IDU exhibited heightened maturation (CD83) compared with control uninfected donors ($P = 0.0011$, $n = 12$). When stimulated in vitro, both PDCs and NK cells from EU-IDU individuals maintained strong effector cell function and did not exhibit signs of exhaustion. Increased maturation of PDCs is associated with heightened NK activation in EU-IDU individuals suggesting that both members of the innate compartment may contribute to resistance from HIV-1 infection in EU-IDU. Tomescu C, Duh FM, Lanier MA, Kapalko A, Mounzer KC, Martin MP, Carrington M, Metzger DS, Montaner LJ. Increased plasmacytoid dendritic cell maturation and natural killer cell activation in HIV-1 exposed, uninfected intravenous drug users. *AIDS*. 2010 Sep 10; 24(14): 2151-2160.

Phase 2a Study of the CCR5 Monoclonal Antibody PRO 140 Administered Intravenously to HIV-Infected Adults

The anti-CCR5 antibody PRO 140 has shown potent and prolonged antiretroviral activity in subjects infected with CCR5-tropic (R5) HIV-1. Prior studies have examined single intravenous doses ranging up to 5 mg/kg of body weight or up to three subcutaneous doses ranging up to 324 mg. The authors report the results of a randomized, double-blind, placebo-controlled trial that examined the antiviral activity, tolerability, and pharmacokinetics of single 5-mg/kg and 10-mg/kg intravenous infusions of PRO 140 in 31 treated subjects. Eligibility criteria included HIV-1 RNA levels of $>5,000$ copies/ml, CD4(+) cell counts of $>300/\mu\text{l}$, no antiretroviral therapy for ≥ 12 weeks, and detection of only R5 HIV-1 in the original Trofile assay. Following poststudy testing with an enhanced-sensitivity Trofile assay, one subject treated with 10 mg/kg was reclassified as having dual/mixed-tropic virus at screening, and the data for that subject were censored from efficacy analyses. The mean maximum reduction of the HIV-1 RNA level from the baseline level was 1.8 \log_{10} units for both the 5-mg/kg and 10-mg/kg doses ($P < 0.0001$ relative to placebo). Viral loads reached their nadir at day 12 posttreatment and remained significantly ($P < 0.01$) reduced through day 29 for both PRO 140 dose groups. Treatment was generally well tolerated, with no dose-limiting toxicity being observed. Peak serum concentrations and overall exposures increased proportionally with dose. In summary, single 5-mg/kg and 10-mg/kg doses of PRO 140 exhibited potent, long-lived antiviral activity and were generally well tolerated. The findings further delineate the safety and antiviral properties of this novel, long-acting antiretroviral agent. Jacobson JM, Lalezari JP, Thompson MA, Fichtenbaum CJ, Saag MS, Zingman BS, D'Ambrosio P, Stambler N, Rotshteyn Y, Marozsan AJ, Maddon PJ, Morris SA, Olson WC. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. *Antimicrob Agents Chemother*. 2010 Oct; 54(10): 4137-4142. Epub 2010 Jul 26.

Drug Interactions Associated with Methadone, Buprenorphine, Cocaine, and HIV Medications: Implications for Pregnant Women

Pregnancy in substance-abusing women with HIV/AIDS presents a complex clinical challenge. Opioid-dependent women need treatment with opioid therapy during pregnancy to protect the health of mother and developing fetus. However, opioid therapies, methadone and buprenorphine, may have drug interactions with some HIV medications that can have adverse effects leading to suboptimal clinical outcomes. Further, many opioid-dependent individuals have problems with other forms of substance abuse, for example, cocaine abuse, that could also contribute to poor clinical outcomes in a pregnant woman. Physiological changes, including increased plasma volume and increased hepatic and renal blood flow, occur in the pregnant woman as the

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pregnancy progresses and may alter medication needs with the potential to exacerbate drug interactions, although there is sparse literature on this issue. Knowledge of possible drug interactions between opioids, other abused substances such as cocaine, HIV therapeutics, and other frequently required medications such as antibiotics and anticonvulsants is important to assuring the best possible outcomes in the pregnant woman with opioid dependence and HIV/AIDS. Elinore F. McCance-Katz. Drug interactions associated with methadone, buprenorphine, cocaine, and HIV medications: Implications for pregnant women. *Life Sci.* 2010 Oct 19 [Epub ahead of print].

Inadequate Vitamin D Exacerbates Parathyroid hormone Elevations in Tenofovir Users

Parathyroid hormone (PTH) elevations are associated with reduced bone mineral density and adverse health outcomes and have been reported in patients with HIV infection. The authors examined the impact of vitamin D status and tenofovir (TDF) use on PTH levels among HIV-infected patients receiving combination antiretroviral therapy (cART). Demographics, medication and supplement use, and clinical data, including 25-hydroxyvitamin D [25(OH)D] and PTH, were collected on 45 HIV-infected men on ART. Suboptimal vitamin D status was defined as 25(OH)D < 30 ng/ml. The relationship between antiretroviral agents, suboptimal 25(OH)D, and PTH levels was examined. Among subjects with suboptimal vitamin D status, PTH values greater than or equal to the ULN (87 pg/ml) were more common among TDF users than nonusers: 41% versus 0% ($p = 0.018$); and median PTH was higher in TDF users: 80 pg/ml versus 55 pg/ml ($p = 0.02$). Among TDF users, PTH was higher in the group with suboptimal 25(OH)D ($p = 0.045$). Multivariable linear regression showed that PTH was independently and directly related to TDF use ($p = 0.017$) and inversely related to 25(OH)D ($p = 0.017$). PTH was not related to the estimated glomerular filtration rate ($p = 0.9$). In this cross-sectional study of HIV-infected men on ART, the use of TDF and the level of 25(OH)D were independently associated with PTH levels. Because TDF is a potent and widely used antiretroviral drug, information about cofactors that may exacerbate its side effects is of significant clinical value. Childs KE, Fishman SL, Constable C, Gutierrez JA, Wyatt CM, Dieterich DT, Mullen MP, Branch AD. Short communication: Inadequate vitamin D exacerbates parathyroid hormone elevations in tenofovir users. *AIDS Res Hum Retroviruses.* 2010 Aug; 26(8): 855-859.

Interactive Role of Human Immunodeficiency Virus Type 1 (HIV-1) Clade-Specific Tat Protein and Cocaine in Blood-Brain Barrier Dysfunction: Implications for HIV-1-Associated Neurocognitive Disorder

In recent years, increasing interest has emerged to assess the human immunodeficiency virus type 1 (HIV-1) clade C viral pathogenesis due to its anticipated spread in the United States and other western countries. Previous studies suggest that clade C is less neuropathogenic than clade B; however, the underlying mechanism is poorly understood. Additionally, the interactive role of drugs of abuse such as cocaine on clade C-associated neuropathogenesis has not been reported. In the current study, the authors hypothesize that HIV-1 clade-specific Tat proteins exert differential effects on blood-brain barrier (BBB) integrity and cocaine further differentially aggravates the BBB dysfunction. The authors evaluated the effect of Tat B and Tat C and/or cocaine on the BBB integrity using an in vitro model constructed with primary human brain microvascular endothelial cells (HBMECs) and astrocytes. The BBB membrane integrity was measured by transendothelial electrical resistance (TEER) and paracellular permeability was measured by fluorescein isothiocyanate (FITC)-dextran transport assay and monocytes transmigration

across the BBB. Results indicate that Tat B disrupts BBB integrity to a greater extent compared to Tat C and cocaine further differentially exacerbates the BBB dysfunction. This BBB dysfunction was associated with altered expression of tight junction proteins zona occludens (ZO-1) and junctional adhesion molecule (JAM)-2. Thus, these results for the first time delineate the differential role of Tat B and Tat C and/or cocaine in BBB dysfunction, which may be correlated with the clade-specific differences observed in HIV-1-associated neurological disorders. Gandhi N, Saiyed ZM, Napuri J, Samikkannu T, Reddy PV, Agudelo M, Khatavkar P, Saxena SK, Nair MP. Interactive role of human immunodeficiency virus type 1 (HIV-1) clade-specific Tat protein and cocaine in blood-brain barrier dysfunction: implications for HIV-1-associated neurocognitive disorder. *J Neurovirol.* 2010 Aug; 16(4): 294-305.

Analysis of HIV Diversity Using a High-Resolution Melting Assay

HIV viruses are usually genetically homogeneous shortly after infection, and become more heterogeneous over time. The authors developed a high-resolution melting (HRM) assay to analyze HIV diversity without sequencing. Plasma samples from the HIVNET 012 trial were obtained from nine Ugandan mother-infant pairs. DNA amplified from the HIV gag region was analyzed to determine the number of degrees over which the DNA melted (HRM score). HRM gag DNA was also cloned and sequenced (50 clones/mother; 20 clones/infant). The median HRM score for infants (4.3, range 4.2-5.3) was higher than that for control plasmids (3.4, range 3.2-3.8, $p < 0.001$) and lower than that for mothers (5.7, range 4.4-7.7, $p = 0.005$, exact Wilcoxon rank sum test). The intraclass correlation coefficient reflecting assay reproducibility was 94% (95% CI: 89-98%). HRM scores were also compared to sequenced-based measures of HIV diversity; higher HRM scores were associated with higher genetic diversity ($p < 0.001$), complexity ($p = 0.009$), and Shannon entropy ($p = 0.022$), but not with length variation ($p = 0.111$). The HRM assay provides a novel, rapid method for assessing HIV diversity without sequencing. This assay could be applied to any region of the HIV genome or to other genetic systems that exhibit DNA diversity. Towler WI, James MM, Ray SC, Wang L, Donnell D, Mwatha A, Guay L, Nakabiito C, Musoke P, Jackson JB, Eshleman SH. Analysis of HIV diversity using a high-resolution melting assay. *AIDS Res Hum Retroviruses.* 2010 Aug; 26(8): 913-918.

Treatment of Medical, Psychiatric, and Substance-use Comorbidities in People Infected with HIV Who Use Drugs

HIV-infected drug users have increased age-matched morbidity and mortality compared with HIV-infected people who do not use drugs. Substance-use disorders negatively affect the health of HIV-infected drug users, who also have frequent medical and psychiatric comorbidities that complicate HIV treatment and prevention. Evidence-based treatments are available for the management of substance-use disorders, mental illness, HIV and other infectious complications such as viral hepatitis and tuberculosis, and many non-HIV-associated comorbidities. Tuberculosis co-infection in HIV-infected drug users, including disease caused by drug-resistant strains, is acquired and transmitted as a consequence of inadequate prescription of antiretroviral therapy, poor adherence, and repeated interfaces with congregate settings such as prisons. Medication-assisted therapies provide the strongest evidence for HIV treatment and prevention efforts, yet are often not available where they are needed most. Antiretroviral therapy, when prescribed and adherence is at an optimum, improves health-related outcomes for HIV infection and many of its comorbidities, including tuberculosis, viral hepatitis, and renal and cardiovascular disease. Simultaneous clinical management of multiple comorbidities in HIV-infected drug users might result in complex pharmacokinetic drug interactions that must be adequately addressed. Moreover, interventions to improve adherence to treatment, including

integration of health services delivery, are needed. Multifaceted, interdisciplinary approaches are urgently needed to achieve parity in health outcomes in HIV-infected drug users. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *Lancet*. 2010 Jul 31; 376(9738): 367-387.

HIV and Proteinuria in an Injection Drug User Population

Proteinuria is a major determinant of chronic kidney disease. The authors aimed to characterize the prevalence and correlates of proteinuria in a cohort of HIV-infected and uninfected injection drug users. A cross-sectional analysis was performed among 902 injection drug users (273 HIV-infected) in the AIDS Linked to the Intravenous Experience cohort. The primary outcome was proteinuria defined as having a urine protein/creatinine concentration ratio >200 mg/g. Poisson regression with robust variance was used to determine prevalence ratios. Overall, 24.8% of participants had proteinuria; the prevalence was 2.9 times higher among HIV-infected participants (45%) compared with HIV-uninfected participants (16%). In addition, age, health insurance, employment status, hepatitis B and C serostatus, diabetes, and high BP were associated with proteinuria. Neither antiretroviral therapy nor features of illicit drug use history were associated with proteinuria. In multivariate analysis, HIV infection, unemployment, increased age, diabetes, hepatitis C infection, and high BP were significantly associated with a higher prevalence of proteinuria. In an aging, predominantly African-American cohort of injection drug users, the authors found a striking burden of proteinuria that was strongly associated with HIV status. In addition to being a pathway to ESRD, proteinuria is a potent risk factor for cardiovascular morbidity and mortality. Evaluation of aggressive screening and disease-modification strategies in this high-risk population is warranted. Yanik EL, Lucas GM, Vlahov D, Kirk GD, Mehta SH. HIV and proteinuria in an injection drug user population. *Clin J Am Soc Nephrol*. 2010 Oct; 5(10): 1836-1843. Epub 2010 Aug 12.

Follow-Up Care among HIV-Infected Pregnant Women in Mississippi

Data from the Centers for Disease Control and Prevention (CDC) indicate that reproductive-age black women in the Southeast are disproportionately affected by the HIV epidemic. There are few data describing HIV infection, pregnancies, and follow-up care in this population. A retrospective chart review was performed at the Perinatal HIV Service at the University of the Mississippi Medical Center in Jackson, Mississippi, to identify HIV-infected women ³ 18 years of age with deliveries from 1999 to 2006. Optimal follow-up was defined as at least two follow-up visits with an HIV provider within 1 year of delivery. Univariate and multivariate logistic regression analyses were used to identify factors associated with optimal adherence. The investigators identified 274 women with 297 total deliveries. Median age was 25, and 89% were black. Only 37% of women had two or more visits with an HIV provider in the postpartum year. On univariate analysis, presentation before the third trimester was associated with optimal follow-up ($p = 0.04$). On multivariate analyses, presentation before the third trimester was the only variable associated with optimal follow-up (odds ratio [OR] 2.1, $p = 0.02$). The poor follow-up rates in this growing population highlight the critical need for research and development of targeted interventions to improve rates of retention in care, particularly in women with late trimester presentation. Rana AI, Gillani FS, Flanigan TP, Nash BT, Beckwith CG. *J Women's Health (Larchmt)*. 2010 Oct; 19(10): 1863-1867.

Opportunities to Diagnose, Treat, and Prevent HIV in the Criminal

Justice System

Persons involved with the criminal justice system are at risk for HIV and other transmissible diseases due to substance use and related risk behaviors. Incarceration provides a public health opportunity to test for HIV, viral hepatitis, and other sexually transmitted infections, provide treatment such as highly active antiretroviral therapy, and link infected persons to longitudinal comprehensive HIV care upon their release for such comorbidities as addiction and mental illness. Delivering health interventions inside prisons and jails can be challenging, yet the challenges pale in comparison to the benefits of interventions for inmates and their communities. This article reviews the current state of delivering HIV testing, prevention, treatment, and transition services to incarcerated populations in the United States. It concludes with summary recommendations for research and practice to improve the health of inmates and their communities. Beckwith CG, Zaller ND, Fu JJ, Montague BT, Rich JD. *J Acquir Immune Defic Syndr*. 2010 Dec 1; 55 Suppl 1: S49-55.

Linking HIV-positive Jail Inmates to Treatment, Care, and Social Services after Release: Results from a Qualitative Assessment of the COMPASS Program

Approximately 17% of individuals living with HIV/AIDS pass through the correctional system each year. Jails provide a unique opportunity to diagnose and treat HIV infection among high-risk, transient populations with limited access to medical services. In 2007, the US Health Resources and Services Administration funded a multi-site demonstration project entitled Enhancing Linkages to HIV Primary Care in Jail Settings that aims to improve diagnosis and treatment services for HIV-positive jail detainees and link them to community-based medical care and social services upon release. The investigators performed an evaluation of the Rhode Island demonstration site entitled Community Partnerships and Supportive Services for HIV-Infected People Leaving Jail (COMPASS). Through in-depth qualitative interviews among 20 HIV-positive COMPASS participants in Rhode Island, the authors assessed how COMPASS impacted access to health care and social services utilization. Most individuals were receiving HIV treatment and care services upon enrollment, but COMPASS enhanced linkage to medical care and follow-up visits for HIV and other co-morbidities for most participants. Several participants were successfully linked to new medical services as a result of COMPASS, including one individual newly diagnosed with HIV and another who had been living with HIV for many years and was able to commence highly active antiretroviral therapy (HAART). While many individuals reported that COMPASS support prevented substance abuse relapse, ongoing substance abuse nevertheless remained a challenge for several participants. Most participants enrolled in one or more new social services as a result of COMPASS, including Medicaid, Supplemental Security Income, food assistance, and housing programs. The primary unmet needs of COMPASS participants were access to mental health services and stable housing. Intensive case management of HIV-positive jail detainees enhances access to medical and social support services and helps prevent relapse to substance abuse. Expanding intensive case management programs, public housing, and mental health services for recently released HIV-positive detainees should be public health priorities. Nunn A, Cornwall A, Fu J, Baseman L, Loewenthal H, Beckwith C. *J Urban Health*. 2010 Oct 29. [Epub ahead of print]; *J Acquir Immune Defic Syndr*. 2010 Oct 1 [Epub ahead of print].

Directly Observed Antiretroviral Therapy in Substance Abusers Receiving Methadone Maintenance Therapy Does Not Cause Increased Drug Resistance

Abstract Direct observation of antiretroviral therapy (DOT) can increase adherence rates in HIV-infected substance users, but whether this affects the development of antiretroviral drug resistance has not been fully explored. The authors conducted a 24-week randomized controlled trial of methadone clinic-based antiretroviral DOT compared with treatment as usual (TAU) among antiretroviral-experienced substance users. To examine the development of new resistance mutations, the investigators identified all participants with an amplifiable resistance test at both baseline and either week 8 or week 24. A comparison of the development of new drug resistance mutations between participants in the two arms of the trial was conducted. Among the 77 participants enrolled in the parent trial, antiretroviral DOT was efficacious for improving adherence and decreasing HIV viral load. Twenty-one participants had a detectable HIV viral load at both baseline and a second time point. Of these, nine developed new drug resistance mutations not seen at baseline (three in the DOT arm and six in the TAU arm; $p = 0.27$). Overall, five subjects in the TAU arm developed major mutations correlating with their current antiretroviral regimen, while no subjects in the DOT arm developed such mutations. Direct observation of antiretroviral therapy was associated with improved adherence and viral suppression among methadone maintained HIV-infected substance users, but was not associated with an increase in the development of antiretroviral drug resistance. DOT should be considered for substance users attending methadone maintenance clinics who are at high risk of nonadherence. Brust JC, Litwin AH, Berg KM, Li X, Heo M, Arnsten JH. *AIDS Res Hum Retroviruses*. 2010 Nov 23 [Epub ahead of print].

Heterosexual Anal Sex Reported by Women Receiving HIV Prevention Services in Los Angeles County

This study examined reported heterosexual receptive anal intercourse (HRAI) in a sample of women recruited from HIV prevention providers in Los Angeles County. The majority of women surveyed were Latina and the modal age was 19 years. Women reporting HRAI were more likely to use both injected and non injected drugs and to have sexual partners who injected drugs. Factors associated with HRAI in a multivariate regression model included use of methamphetamine; use of alcohol before, during, or after sex; and use of dental services at the interview agency. Factors inversely associated with heterosexual anal sex were being African American (compared with Latina) and endorsing the use of condoms for episodes of vaginal sex from start to finish. The authors conclude that HIV prevention providers in Los Angeles County should be aware of the need for basic prevention messages concerning condom use and injection behavior in young Latina women. Reynolds GL, Fisher DG, Napper LE, Fremming BW, Jansen MA. *Womens Health Issues*. 2010 Nov-Dec; 20(6): 414-419.

Who Chooses a Rapid Test for HIV in Los Angeles County, California?

The purpose of this study was to determine who chooses a rapid test for HIV when given a choice in a community-based or mobile van setting in Long Beach, California. Individuals were given a choice of either rapid or standard HIV testing either alone or in conjunction with testing for sexually transmitted diseases (STD). Of the 2,752 HIV tests performed between March 2005 and March 2009, 917 (33%) were rapid tests. Preference for rapid HIV testing was among men who have sex with men (MSM), who reported using alcohol in the last 48 hr but who did not endorse the use of illicit drugs; individuals reporting sex trading were also more likely to choose the rapid HIV test. African Americans, regardless of sexual identification, were significantly less likely to choose an HIV rapid test. Strategies are needed to encourage HIV rapid testing among both non-injection and injection drug users, and other at-risk groups. Marsh KA, Reynolds GL, Rogala BE, Fisher DG, Napper LE. *Eval Health Prof*.

2010 Jun; 33(2): 177-196. Epub 2010.

Protective Interleukin-28B Genotype Affects Hepatitis C Virus Clearance, But Does Not Contribute to HIV-1 Control in a Cohort of African-American Elite Controllers/ Suppressors

The authors tested the hypothesis that a single nucleotide polymorphism (SNP) located near the interleukin-28B gene is associated with the control of hepatitis C virus and HIV-1 replication in elite controllers/suppressors. They show here that the protective genotype is not overrepresented in elite controllers/suppressors compared with HIV-1-seronegative patients and HIV-1-infected patients with viral loads more than 10 000 copies/ml. Thus, it appears that this SNP is not associated with the elite control of HIV-1 infection. Salgado M, Kirk GD, Cox A, Rutebemberwa A, Higgins Y, Astemborski J, Thomas DL, Thio CL, Sulkowski MS, Blankson JN. Protective interleukin-28B genotype affects hepatitis C virus clearance, but does not contribute to HIV-1 control in a cohort of African-American elite controllers/suppressors. *AIDS*. 2010 Nov 19 [Epub ahead of print].

Potential Role for Interleukin-28B Genotype in Treatment Decision-Making in Recent Hepatitis C Virus Infection

Polymorphisms in the IL28B (interleukin-28B) gene region are important in predicting outcome following therapy for chronic hepatitis C virus (HCV) infection. The authors evaluated the role of IL28B in spontaneous and treatment-induced clearance following recent HCV infection. The Australian Trial in Acute Hepatitis C (ATAHC) was a study of the natural history and treatment of recent HCV, as defined by positive anti-HCV antibody, preceded by either acute clinical HCV infection within the prior 12 months or seroconversion within the prior 24 months. Factors associated with spontaneous and treatment-induced HCV clearance, including variations in IL28B, were assessed. Among 163 participants, 132 were untreated ($n = 52$) or had persistent infection (infection duration ≥ 26 weeks) at treatment initiation ($n = 80$). Spontaneous clearance was observed in 23% (30 of 132 participants). In Cox proportional hazards analysis (without IL28B), HCV seroconversion illness with jaundice was the only factor predicting spontaneous clearance (adjusted hazards ratio = 2.86; 95% confidence interval = 1.24, 6.59; $P = 0.014$). Among participants with IL28B genotyping ($n = 102$ of 163 overall and 79 of 132 for the spontaneous clearance population), rs8099917 TT homozygosity (versus GT/GG) was the only factor independently predicting time to spontaneous clearance (adjusted hazard ratio = 3.78; 95% confidence interval = 1.04, 13.76; $P = 0.044$). Participants with seroconversion illness with jaundice were more frequently rs8099917 TT homozygotes than other (GG/GT) genotypes (32% versus 5%, $P = 0.047$). Among participants adherent to treatment and who had IL28B genotyping ($n = 54$), sustained virologic response was similar among TT homozygotes (18 of 29 participants, 62%) and those with GG/GT genotype (16 of 25, 64%, $P = 0.884$). During recent HCV infection, genetic variations in IL28B region were associated with spontaneous but not treatment-induced clearance. Early therapeutic intervention could be recommended for individuals with unfavorable IL28B genotypes. Grebely J, Petoumenos K, Hellard M, Matthews GV, Suppiah V, Applegate T, Yeung B, Marks P, Rawlinson W, Lloyd AR, Booth D, Kaldor JM, George J, Dore GJ, ATAHC Study Group. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology*. 2010 Oct; 52(4): 1216-1224.

Factors Associated with Uptake of Treatment for Recent Hepatitis C Virus Infection In a Predominantly Injecting Drug User Cohort: The ATAHC Study

Despite that the majority of hepatitis C virus (HCV) infection occurs among injection drug users (IDUs), little is known about HCV treatment uptake in this group, particularly during recent infection. The authors evaluated uptake of treatment for recent HCV infection, including associated factors, within a population predominantly made up of IDUs. The Australian Trial in Acute Hepatitis C was a study of the natural history and treatment of recent HCV infection. All participants with detectable HCV RNA at screening were offered HCV treatment, assessed for eligibility and those initiating treatment were identified. Logistic regression analyses were used to identify predictors of HCV treatment uptake. Between June 2004 and February 2008, 163 were enrolled, with 146 positive for HCV RNA at enrolment. The mean age was 35 years, 77% (n = 113) participants had ever injected illicit drugs and 23% (n = 34) reported having ever received methadone or buprenorphine treatment. The uptake of HCV treatment was 76% (111 of 146) among those who were eligible on the basis of positive HCV RNA. Estimated duration of HCV infection (OR = 1.03 per week, 95% CI = 1.00-1.06, P = 0.035) and log₁₀ HCV RNA (OR = 1.92 per log₁₀ increase, 95% CI = 1.36-2.73, P < 0.001) were independently associated with treatment uptake whereas injection drug use was not. This study demonstrates that a high uptake of HCV treatment can be achieved among participants with recently acquired HCV infection. Decisions about whether to initiate treatment for recently acquired HCV were mainly driven by clinical factors, rather than factors related to sociodemographics or injecting behaviors. Grebelya J, Petoumenos K, Matthews GV, Haber P, Marks P, Lloyd AR, Kaldor JM, Dorea GJ, Hellard M. Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATACH Study. *Drug and Alcohol Dependence*. 2010; 107: 244-249.

Hepatitis C Virus Infection of Neuroepithelioma Cell Lines

Hepatitis C virus (HCV) establishes chronic infections in 3% of the world's population. Infection leads to progressive liver disease; hepatocytes are the major site of viral replication in vivo. However, chronic infection is associated with a variety of extrahepatic syndromes, including central nervous system (CNS) abnormalities. The authors therefore screened a series of neural and brain-derived cell lines for their ability to support HCV entry and replication. The authors used a panel of neural-derived cell lines, HCV pseudoparticles (HCVpp), and an infectious, HCV JFH-1 cell-culture system (HCVcc) to assess viral tropism. Two independently derived neuroepithelioma cell lines (SK-N-MC and SK-PN-DW) permitted HCVpp entry. In contrast, several neuroblastoma, glioma, and astrocytoma cell lines were refractory to HCVpp infection. HCVcc infected the neuroepithelioma cell lines and established a productive infection. Permissive neuroepithelioma cells expressed CD81, scavenger receptor BI (SR-BI), and the tight junction proteins Claudin-1 (CLDN1) and occludin, whereas nonpermissive neural cell lines lacked CLDN1 and, in some cases, SR-BI. HCVpp infection of the neuroepithelioma cells was neutralized by antibodies to CD81, SR-BI, CLDN1, and HCV E2. Furthermore, anti-CD81, interferon, and the anti-NS3 protease inhibitor VX-950 significantly reduced HCVcc infection of neuroepithelioma and hepatoma cells. Neuroepithelioma-derived cell lines express functional receptors that support HCV entry at levels comparable to those of hepatoma cells. HCV infection in vitro is not restricted to hepatic-derived cells, so HCV might infect cells of the CNS in vivo. Fletcher NF, Yang JP, Farquhar MJ, Hu K, Davis C, He Q, Dowd K, Ray SC, Krieger SE, Neyts J, Baumert TF, Balfe P, McKeating JA, Wong-Staal F. Hepatitis C virus infection of neuroepithelioma cell lines. *Gastroenterology*. 2010 Oct; 139(4): 1365-1374. Epub 2010 Jun 9.

Acceleration of Hepatitis C Virus Envelope Evolution in Humans is Consistent with Progressive Humoral Immune Selection During

the Transition From Acute to Chronic Infection

During the transition from acute to chronic infection in individuals persistently infected with hepatitis C virus (HCV), cellular responses initiate within the first 6 months of primary infection and collapse thereafter, whereas humoral responses activate later during the chronic phase. Whether and how this deviation of immune responses specifically influences HCV evolution are unknown. To determine the pattern of HCV evolution during this critical period, the authors conducted extensive sequence analysis on annual clonal hemigenomic sequences for up to 3 years in six well-characterized subjects, using statistical methods that accounted for repeated measures. Significantly different evolutionary rates were observed in envelope versus nonenvelope genes, with an increasing rate of nonsynonymous change (dN) in envelope genes and a stable dN in nonenvelope genes ($P = 0.006$). The ratio of the envelope to nonenvelope nonsynonymous rate increased from 2 in year 1 to 5 in years 2 and 3. Centripetal changes (reversions toward matching of the worldwide subtype 1a consensus sequence) were frequently observed during the 3-year transition from acute infection to chronicity, even in the presence of neutralizing antibody (NAb) pressure. Remarkably, sequences of hypervariable region 1 (HVR1) remained stable for up to 21 months in the absence of NAb pressure in one subject, followed by rapid changes that were temporally associated with the detection of NAb responses, which strongly suggests that HVR1 evolution is shaped by NAb pressure. These data provide the first systematic estimates of HCV evolutionary rates in multiple genes during early infection in vivo and provide additional evidence for deterministic, rather than random, evolution of HCV. Liu L, Fisher BE, Dowd KA, Astemborski J, Cox AL, Ray SC. Acceleration of hepatitis C virus envelope evolution in humans is consistent with progressive humoral immune selection during the transition from acute to chronic infection. *J Virol.* 2010 May; 84(10): 5067-5077. Epub 2010 Mar 3.

Sustained Long-Term Antiviral Maintenance Therapy in HCV/HIV Co-infected Patients (SLAM-C)

Hepatitis C virus (HCV)/HIV coinfection treatment is suboptimal with low SVR rates to standard therapies. A multicenter randomized clinical trial designed to assess the efficacy/safety of pegylated interferon maintenance therapy was performed by the National Institutes of Health-funded Aids Clinical Trials Group network. HCV treatment-naïve and nonresponding interferon-experienced subjects with confirmed HCV and HIV, CD4 >200 cells per cubic millimeter, and at least stage 1 fibrosis were enrolled and treated for 12 weeks with pegylated interferon alfa 2a 180 mcg per week (PEG) + weight-based ribavirin to determine response status. Nonresponder subjects (failure to clear HCV RNA or achieve 2-log drop) underwent liver biopsy and were randomized to receive full dose PEG or observation only for 72 weeks. Paired biopsies were evaluated by a central pathologist. Three hundred thirty subjects were enrolled; median age was 48 years; 43% white, 37% black, non-Hispanic; 83% male; CD4+ 498 cells per cubic millimeter; 32% were interferon experienced; 74% had entry HIV RNA <50 copies per milliliter. early virologic responder was observed in 55.9% and 42.5% achieved cEVR. A planned interim analysis of occurred when 84 subjects were randomized. With data on 40 paired biopsies available, a safety monitoring board stopped the trial due to lack of fibrosis progression (median = 0 Metavir units/year) in the observation arm. Lack of fibrotic progression in the control arm was unexpected and may represent a short-term PEG/ribavirin therapy effect, high levels of HIV viral suppression, and use of antiretroviral regimens that may be less toxic than prior generations of therapy. Sherman KE, Andersen JW, Butt AA, Umbleja T, Alston B, Koziel MJ, Peters MG, Sulkowski M, Goodman ZD, Chung RT, for the AIDS Clinical Trials Group A5178 Study Team. Sustained long-term antiviral maintenance therapy in HCV/HIV co-infected patients (SLAM-C). *J Acquir Immune Defic Syndr.* 2010

Oct 1. [Epub ahead of print]

Incidence and Rates of Transition to Injecting among Mexican American (MA) Non-Injecting Heroin Users (NIU)

In a prospective cohort study of street-recruited MA-NIU in San Antonio, Texas, 2002-2005, participants were administered structured interviews and tested for Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The analysis sample comprised former injection drug users (last injected >6 months ago, n=47) and those who had never injected drugs and tested HCV negative (n=219). A transition to injecting was defined as the first injection of illicit drugs since baseline interview. Transition rates were based on person-years at-risk (PYAR). Proportional hazards regression was used to estimate crude and adjusted (for significant differences between former and never injectors) hazard ratios and 95% confidence intervals of injecting history on transitioning to injecting. Sixty-three (24%) participants transitioned to injecting at a rate of 22.3/100 PYAR (95% CI: 17.2-28.2). Former-injectors were significantly more likely to transition than never injectors (43% or 20/47 vs. 20% or 43/219; $p < 0.001$), and did so at a faster rate (40.4/100 PYAR, 95% CI: 24.6-60.0 vs. 18.5/100 PYAR, 95% CI: 13.4-24.4), with the crude HR=1.931 (95% CI: 1.116, 3.341) and adjusted HR=2.263 (95% CI: 1.192-4.294). The rate of transitioning to injecting was high and greater among former injectors. Of particular concern is the high rate of injecting initiation among never injectors. Future analyses will examine factors associated with injecting initiation, including individual susceptibility and behaviors, social networks, and the cultural and drug market context. Valdez A, Neaigus A, Kaplan C, Cepeda A. High rates of transition to injecting drug use among Mexican American non-injecting heroin users in San Antonio, Texas. *Drug and Alcohol Dependence*. 2010 Nov 12. Epub ahead of print.

Insulin Resistance Predicts Re-treatment Failure in an Efficacy Study of Peginterferon- α -2a and Ribavirin in HIV/HCV Co-infected Patients

Few studies have evaluated the efficacy of HCV re-treatment and the predictors of response in HIV/HCV co-infected patients. The role of insulin resistance as a predictor of response in this population is unknown. The aim of this study is to evaluate the safety and efficacy of pegylated interferon- α -2a and ribavirin in re-treatment of HIV/HCV co-infected patients, predictors of sustained virological response, including insulin resistance, and the relationship between insulin resistance and liver histology. This prospective, multi-centered study included HIV/HCV co-infected patients with prior interferon-based treatment failure. Patients received pegylated interferon- α -2a and ribavirin for 48 weeks. Serum HCV RNA was measured 24 weeks post treatment to assess sustained virological response. Insulin resistance was defined as HOMA-IR > 2. Correlations between baseline insulin resistance and steatosis, and/or cirrhosis were determined. Sustained virological response was achieved in 14/96 (15%) patients. 35% of patients with HOMA-IR < 2 (6/17) achieved sustained virological response vs 14% (5/36) of those with HOMA-IR between 2-4, and 7% (3/41) of those with HOMA-IR > 4 ($p = 0.01$). In multivariable analysis, insulin resistance and \log_{10} HCV RNA were negatively associated with sustained virological response [AOR 0.17; 95% CI 0.05-0.64, $p = 0.009$, and AOR 0.36; 95% CI 0.14-0.93, $p = 0.04$, respectively]. Steatosis and cirrhosis correlated with insulin resistance ($p = 0.02$ and 0.03, respectively) but neither independently predicted sustained virological response. Discontinuations due to severe adverse events occurred in 8% of cases, and 2 patients died of unrelated causes. In HIV/HCV co-infected patients undergoing re-treatment, sustained virological response rate is low; those patients without insulin resistance are significantly more likely to achieve sustained virological response. Vachon ML, Factor SH, Branch AD, Fiel MI, Rodriguez-Torres M, BrŠu

N, Sterling RK, Slim J, Talal AH, Dieterich DT, Sulkowski MS. J Hepatol. 2011 Jan; 54(1): 41-47. Epub 2010 Aug 21.

Candidate Hepatitis C Vaccine Trials and People Who Inject Drugs: Challenges and Opportunities

People who inject drugs (PWID) are at high risk of HCV. Limited evidence of the effectiveness of prevention interventions and low uptake of treatment in this group highlight the need for increased investment in biomedical interventions, notably safe and efficacious vaccines. While several candidates are currently in development, field trials in PWID present challenges, including ethical issues associated with trial literacy, informed consent and standards of care. Significant biological and social factors and differences between HIV and HCV suggest that HCV warrants targeted vaccine preparedness research to lay the groundwork for successful implementation of future trials. Maher L, White B, Hellard M, Madden A, Prins M, Kerr T, Page K. Candidate hepatitis C vaccine trials and people who inject drugs: challenges and opportunities. Vaccine. 2010 Oct 21; 28(45): 7273-7278. Epub 2010 Sep 9.

Low Rates of Hepatitis A and B Vaccination in Patients with Chronic Hepatitis C at an Urban Methadone Maintenance Program

Patients with chronic hepatitis C virus (HCV) are at increased risk for complications of liver disease if they become infected with the hepatitis A (HAV) or hepatitis B (HBV) viruses. The authors examined the rates of testing for HAV, HBV, and HCV, as well as rates of vaccination against HAV and HBV in patients with chronic HCV in a random sample (N = 207) of medical records of patients enrolled in a methadone maintenance program. Almost all patients reviewed were tested for HAV, HBV, and HCV. Of the 111 patients with chronic HCV, 53 (48.6%) and 68 (63%) lacked immunity to HAV and HBV, respectively. Of those lacking immunity, 29 (54.7%) and 2 (2.9%) were vaccinated for HAV and HBV, respectively. Despite high rates of testing for HAV, HBV, and HCV at a methadone maintenance program, approximately half of those with chronic HCV eligible for the HAV vaccine received it, and few of those eligible for HBV vaccine received it. Felsen UR, Fishbein DA, Litwin AH. Low rates of hepatitis A and B vaccination in patients with chronic hepatitis C at an urban methadone maintenance program. J Addict Dis. 2010 Oct; 29(4): 461-465.

Chemical Combinations Elucidate Pathway Interactions and Regulation Relevant to Hepatitis C Replication

The search for effective Hepatitis C antiviral therapies has recently focused on host sterol metabolism and protein prenylation pathways that indirectly affect viral replication. However, inhibition of the sterol pathway with statin drugs has not yielded consistent results in patients. Here, the authors present a combination chemical genetic study to explore how the sterol and protein prenylation pathways work together to affect hepatitis C viral replication in a replicon assay. In addition to finding novel targets affecting viral replication, their data suggest that the viral replication is strongly affected by sterol pathway regulation. There is a marked transition from antagonistic to synergistic antiviral effects as the combination targets shift downstream along the sterol pathway. The authors also show how pathway regulation frustrates potential hepatitis C therapies based on the sterol pathway, and reveal novel synergies that selectively inhibit hepatitis C replication over host toxicity. In particular, combinations targeting the downstream sterol pathway enzymes produced robust and selective synergistic inhibition of hepatitis C replication. Their findings show how combination chemical genetics can reveal critical pathway connections relevant to viral replication, and can identify potential treatments

with an increased therapeutic window. Owens CM, Mawhinney C, Grenier JM, Altmeyer R, Lee MS, Borisy AA, Lehár J, Johansen LM. Chemical combinations elucidate pathway interactions and regulation relevant to Hepatitis C replication. *Mol Syst Biol.* 2010 Jun 8; 6: 375.

Waterpipe Tobacco Smoking: An Emerging Health Crisis in the United States

To examine the prevalence and potential health risks of waterpipe tobacco smoking. A literature review was performed to compile information relating to waterpipe tobacco smoking. Waterpipe tobacco smoking is increasing in prevalence worldwide; in the United States, 10-20% of some young adult populations are current waterpipe users. Depending on the toxicant measured, a single waterpipe session produces the equivalent of at least 1 and as many as 50 cigarettes. Misconceptions about waterpipe smoke content may lead users to underestimate health risks. Inclusion of waterpipe tobacco smoking in tobacco control activities may help reduce its spread. Cobb C, Ward KD, Maziak W, Shihadeh AL, Eissenberg T. Waterpipe tobacco smoking: an emerging health crisis in the United States. *Am J Health Behav.* 2010 May-Jun; 34(3): 275-285.

Are Maternal Depression or Symptom Severity Associated with Breastfeeding Intention or Outcomes?

Breastfeeding confers many health benefits to mothers and infants, while depression negatively affects mothers and infants. The aims of this study were to determine relationships between (1) major depressive disorder (MDD) and depressive symptom severity during pregnancy and breastfeeding intention; (2) MDD and depressive symptom severity during pregnancy and breastfeeding initiation and status at 2 and 12 weeks; and (3) serotonin reuptake inhibitor (SRI) use and breastfeeding intention, initiation, and status at 2 and 12 weeks. Women were followed prospectively from pregnancy through 12 weeks postpartum for infant feeding intention (breast, breast and formula, formula, and uncertain), feeding practices and MDD (Structured Clinical Interview for DSM-IV Disorders), and depressive symptom severity (Hamilton Depression Rating Scale). Bivariate analyses and multivariable regression modeling were conducted. The study was conducted from July 2004 to September 2007. Study participants (intention n = 168, initiation n = 151, 2 weeks n = 137, 12 weeks n=103) were well educated (63% college degrees), older (49% > or = 31 years), and predominantly white (77%). At enrollment, 23% had MDD, 21% had significant depressive symptoms, and 16% were taking an SRI. Neither MDD nor depressive symptom severity in pregnancy was related to breastfeeding intention, initiation or duration at 2 and 12 weeks. Intention to exclusively breastfeed was the most significant predictor of breastfeeding initiation and duration. SRI use in pregnancy was negatively associated with breastfeeding intention. SRI use at 2 weeks was negatively associated with 12-week breastfeeding status. Pregnancy is the optimal time to intervene to increase breastfeeding rates. Future research should identify strategies to overcome breastfeeding barriers posed by SRI use. Bogen DL, Hanusa BH, Moses-Kolko E, Wisner KL. Are maternal depression or symptom severity associated with breastfeeding intention or outcomes? *J Clin Psychiatry.* 2010 Aug; 71(8): 1069-1078. Epub 2010 Jun 15.

Current Aspects of Formulation Efforts and Pore Lifetime Related to Microneedle Treatment of Skin

The efficacy of microneedles in the area of transdermal drug delivery is well documented. Multiple studies have shown that enhancement of skin permeation by means of the creation of microscopic pores in the stratum

corneum can greatly improve the delivery rates of drugs. However, skin pretreatment with microneedles is not the only factor affecting drug transport rates. Other factors, including drug formulation and rate of micropore closure, are also important for optimizing delivery by this route. This review aims to highlight work that has been done in these areas, with an emphasis on drug formulation parameters that affect transdermal flux. This review creates an appreciation for the many factors affecting microneedle-enhanced delivery. Most results clearly indicate that microneedle skin pretreatment by itself may have different effects on drug transport depending on the formulation used, and formulation characteristics have different effects on the transport through untreated skin and microneedle-treated skin. Several formulation approaches are reported to optimize microneedle-enhanced drug delivery, including co-solvent use, vesicular, nanoparticulate and gel systems. In addition to well-established factors that affect microneedle-assisted delivery (geometry, type of microneedle, etc.), formulation and pore viability are also critical factors that must be considered. Milewski M, Brogden NK, Stinchcomb AL. Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin. *Expert Opin Drug Deliv.* 2010 May; 7(5): 617-629.

Transdermal Delivery of Naltrexol and Skin Permeability Lifetime After Microneedle Treatment in Hairless Guinea Pigs

Controlled-release delivery of 6-beta-naltrexol (NTXOL), the major active metabolite of naltrexone, via a transdermal patch is desirable for treatment of alcoholism. Unfortunately, NTXOL does not diffuse across skin at a therapeutic rate. Therefore, the focus of this study was to evaluate microneedle (MN) skin permeation enhancement of NTXOL's hydrochloride salt in hairless guinea pigs. Specifically, these studies were designed to determine the lifetime of MN-created aqueous pore pathways. MN pore lifetime was estimated by pharmacokinetic evaluation, transepidermal water loss (TEWL) and visualization of MN-treated skin pore diameters using light microscopy. A 3.6-fold enhancement in steady-state plasma concentration was observed in vivo with MN treated skin with NTXOL.HCl, as compared to NTXOL base. TEWL measurements and microscopic evaluation of stained MN-treated guinea pig skin indicated the presence of pores, suggesting a feasible nonlipid bilayer pathway for enhanced transdermal delivery. Overall, MN-assisted transdermal delivery appears viable for at least 48 h after MN-application. Banks SL, Pinninti RR, Gill HS, Paudel KS, Crooks PA, Brogden NK, Prausnitz MR, Stinchcomb AL. Transdermal delivery of naltrexol and skin permeability lifetime after microneedle treatment in hairless guinea pigs. *J Pharm Sci.* 2010 Jul; 99(7): 3072-3080.

Methamphetamine Causes Mitochondrial Oxidative Damage in Human T Lymphocytes Leading to Functional Impairment

Methamphetamine (METH) abuse is known to be associated with an inordinate rate of infections. Although many studies have described the association of METH exposure and immunosuppression, so far the underlying mechanism still remains elusive. In this study, the authors present evidence that METH exposure resulted in mitochondrial oxidative damage and caused dysfunction of primary human T cells. METH treatment of T lymphocytes led to a rise in intracellular calcium levels that enhanced the generation of reactive oxygen species. TCR-CD28 linked calcium mobilization and subsequent uptake by mitochondria in METH-treated T cells correlated with an increase in mitochondrion-derived superoxide. Exposure to METH-induced mitochondrial dysfunction in the form of marked decrease in mitochondrial membrane potential, increased mitochondrial mass, enhanced protein nitrosylation and diminished protein levels of complexes I, III, and IV of the electron transport chain. These changes paralleled reduced IL-2 secretion and T cell proliferative responses after TCR-CD28 stimulation indicating impaired T cell function.

Furthermore, antioxidants attenuated METH-induced mitochondrial damage by preserving the protein levels of mitochondrial complexes I, III, and IV. Altogether, our data indicate that METH can cause T cell dysfunction via induction of oxidative stress and mitochondrial injury as underlying mechanism of immune impairment secondary to METH abuse. Potula R, Hawkins BJ, Cenna JM, Fan S, Dykstra H, Ramirez SH, Morsey B, Brodie MR, Persidsky Y. Methamphetamine causes mitochondrial oxidative damage in human T lymphocytes leading to functional impairment. *J Immunol.* 2010 Sep 1; 185(5): 2867-2876. Epub 2010 Jul 28.

Specific Cross-Reaction of Anti-dsDNA Antibody with Platelet Integrin GPIIIa49-66

Anti-platelet autoantibodies are frequently found in systemic lupus erythematosus (SLE) patients and contribute to the development of SLE-associated immunologic thrombocytopenia (SLE-ITP). Although the correlation of anti-dsDNA autoantibody with platelet-associated antibody has been reported, the potential mechanism underlying such a correlation is incompletely understood. The authors have reported that anti-platelet integrin GPIIIa49-66 (CAPESIEFPVSEARVLED) autoantibodies play a major role in the development of HIV-1-related thrombocytopenia (HIV-1-ITP). The strong negative charge of GPIIIa49-66 prompts us to investigate whether GPIIIa49-66 can be an epitope mimicking dsDNA. The authors report here that anti-GPIIIa49-66 antibodies are found in three out of nine SLE-ITP patients. Double-stranded (ds) DNA competitively inhibited the binding of purified patient anti-dsDNA antibodies to GPIIIa49-66 peptide. Both polyclonal and monoclonal anti-GPIIIa49-66 antibodies are able to cross-react with dsDNA. Consistent with previous reports, the DNA binding activities of anti-GPIIIa49-66 antibodies are mainly dependent on the positively charged amino acid in the heavy-chain complementarity-determining region 3 (HCDR3). The HCDR3 of human SLE anti-dsDNA monoclonal antibody (mAb) 412.67 demonstrates a similar positively charged amino acid chain orientation compared with that of anti-GPIIIa49-66 mAb A11, and it cross-reacts with GPIIIa49-66 peptide. Purified anti-GPIIIa49-66 antibodies from SLE-ITP patients are able to induce platelet fragmentation in vitro and to induce thrombocytopenia in vivo. Thus, our data suggest that specific epitope cross-reaction between GPIIIa49-66 and dsDNA could be a mechanism involved in the development of SLE-associated thrombocytopenia. Zhang W, Dang S, Wang J, Nardi MA, Zan H, Casali P, Li Z. Specific cross-reaction of anti-dsDNA antibody with platelet integrin GPIIIa49-66. *Autoimmunity.* 2010 Dec; 43(8): 682-689. Epub 2010 Sep 9.

Comparison of Puberty and Psychosocial Adjustment Between Taiwanese Adolescent Females With and Without Diabetes

The aims of this study were to (1) determine the differences in puberty and psychosocial adjustment among Taiwanese adolescent females with and without type 1 diabetes mellitus, and (2) examine the interaction between pubertal timing and diabetes in relation to its effect on adolescent's psychosocial adjustment. Rapid physical and sexual changes during puberty elicit a wide array of psychosocial adjustments. The effects of pubertal changes among adolescent females with type 1 diabetes mellitus on psychosocial adjustment are unknown. This study used a comparative, case-controlled design. A total of 82 adolescent females, aged 10-17, were recruited for the study. Forty-one adolescents with type 1 diabetes mellitus were age-matched to 41 adolescents without type 1 diabetes mellitus. Adolescents' psychosocial adjustment, including internalising and externalising behaviours, was assessed using the Child Behaviour Checklist (parental report) and the Youth Self-Report (individual self-report). The self-reported Pubertal Development Scale was used to measure adolescents' puberty, including onset of menses, age at menarche and pubertal timing. When compared to their counterparts, adolescent females

with type 1 diabetes mellitus reported a delayed menarche and a delayed puberty. Females with type 1 diabetes mellitus had significantly greater internalising and externalising behaviours than their counterparts according to parental reports. Onset of menses and adolescent self-reported psychosocial adjustment were not different between the two groups. Interaction analyses showed that the association between pubertal timing and internalising behaviours was related to the presence of diabetes. According to parental reports, early pubertal timing had positive effects on internalising behaviours for adolescent females with type 1 diabetes mellitus not for adolescent females without type 1 diabetes mellitus. A multi-informant approach is suggested when health care professionals assess adolescent psychosocial adjustment. Health care professionals must provide female teenagers with information and opportunities to discuss the impact of type 1 diabetes mellitus on their puberty and psychosocial adjustment. Hsu YY, Dorn LD, Sereika SM. Comparison of puberty and psychosocial adjustment between Taiwanese adolescent females with and without diabetes. *J Clin Nurs.* 2010 Oct; 19(19-20): 2704-2712.

Morningness/Eveningness, Pubertal Timing, and Substance Use in Adolescent Girls

The purpose of this study was to examine the associations between Morningness/Eveningness (M/E; a measure of sleep-wake preference) and alcohol, cigarette, and marijuana use as well as the interaction of M/E and pubertal timing. The data represent baseline measures from a longitudinal study examining the association of psychological functioning and smoking with reproductive and bone health in 262 adolescent girls (11-17years). The primary measures used for this study were pubertal timing (measured by age at menarche), the Morningness/Eveningness scale, and substance use (alcohol, cigarettes, and marijuana). Multiple group path modeling showed that there was a significant interaction between pubertal timing and M/E on cigarette use. The direction of the parameter estimates indicated that for the early and on-time groups, Evening preference was associated with more cigarette use. For the late timing group the association was not significant. The results point to the need to consider sleep preference as a characteristic that may increase risk for substance use in adolescents. Negriff S, Dorn LD, Pabst SR, Susman EJ. Morningness/ eveningness, pubertal timing, and substance use in adolescent girls. *Psychiatry Res.* 2010 Jul 29. [Epub ahead of print]

Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Once-Daily Lopinavir/Ritonavir

This study was conducted to examine the pharmacokinetic interactions between buprenorphine/naloxone (BUP/NLX) and lopinavir/ritonavir (LPV/r) in HIV-seronegative subjects chronically maintained on BUP/NLX. This study was an open labeled pharmacokinetic study in twelve HIV-seronegative subjects stabilized on at least 3 weeks of BUP/NLX therapy. Subjects sequentially underwent baseline and steady-state pharmacokinetic evaluation of once-daily LPV/r (800/200 mg). Compared to baseline values, BUP AUC_{0-24h} (46.8 vs. 46.2 ng*hr/mL) and C_{max} (6.54 vs. 5.88 ng/mL) did not differ significantly after achieving steady-state LPV/r. Similar analyses of norBUP, the primary metabolite of BUP, demonstrated no significant difference in norBUP AUC₀₋₂₄ hours (73.7 vs. 52.7 ng x h/mL); however, C_{max} (5.29 vs. 3.11 ng/mL) levels were statistically different (P < 0.05) after LPV/r administration. Naloxone concentrations were similarly unchanged for AUC₀₋₂₄ hours (0.421 vs. 0.374 ng x hr/mL) and C_{max} (0.186 vs. 0.186 ng/mL). Using standardized measures, no objective opioid withdrawal was observed. The AUC₀₋₂₄ hours and C_{min} of LPV in this study did not significantly differ from historical controls (159.6 vs. 171.3 microg x hr/mL) and (2.3 vs. 1.3 microg/mL). The addition of LPV/r to stabilized patients receiving BUP/NLX did not affect buprenorphine pharmacokinetics but did increase the clearance of norbuprenorphine.

Pharmacodynamic responses indicate that the altered norbuprenorphine clearance did not lead to opioid withdrawal. Buprenorphine/naloxone and LPV/r can be safely coadministered without need for dosage modification. Bruce RD, Altice FL, Moody DE, Morse GD, Andrews L, Lin SN, Fang WB, Ma Q, Friedland GH. Pharmacokinetic interactions between buprenorphine/naloxone and once-daily lopinavir/ritonavir. *J Acquir Immune Defic Syndr*. 2010 Aug 15; 54(5): 511-514.

Implications of ER Stress, the Unfolded Protein Response, and Pro- and Anti-Apoptotic Protein Fingerprints in Human Monocyte-Derived Dendritic Cells Treated With Alcohol

Dendritic cells (DCs) are responsible for the activation of T cells and B cells. There is accumulating evidence that psychoactive substances such as alcohol can affect immune responses. The authors hypothesize that this occurs by modulating changes in proteins triggering a process known as unfolded protein response (UPR). This process protects cells from the toxic effects of misfolded proteins responsible for causing endoplasmic reticulum (ER) stress. Although much is known about ER stress, little is understood about the consequences of ethanol use on DC's protein expression. In this study, the authors investigated alterations in the proteins of human monocyte-derived dendritic cells (MDDC) treated with 0.1% of alcohol by two-dimensional (2D) gel electrophoresis followed by liquid chromatography-tandem mass spectrometry, protein identification, and confirmation at the gene expression level by qRT-PCR. Proteomes of related samples demonstrated 32 differentially expressed proteins that had a 2-fold or greater change in expression (18 spots were up-regulated and 14 were down-regulated), compared to the control cultures (untreated cells). Alcohol significantly changed the expression of several components of the UPR stress-induced pathways that include chaperones, ER stress, antioxidant enzymes, proteases, alcohol dehydrogenase, cytoskeletal and apoptosis-regulating proteins. qRT-PCR analyses highlighted the enhanced expression of UPR and antioxidant genes that increased (18 hours) with alcohol treatment. Results of these analyses provide insights into alcohol mechanisms of regulating DC and suggest that alcohol induced specifically the UPR in DC. The authors speculate that activation of a UPR by alcohol may protect the DC from oxidant injury but may lead to the development of alcohol-related diseases. Boukli NM, Saiyed ZM, Ricaurte M, Rodriguez JW, Ríos Olivares E, Cubano LA, Nair MP. *Alcohol Clin Exp Res*. 2010 Dec; 34(12): 2081-2088. Epub 2010 Sep 22.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Services Research

Use of Medications in Publicly Funded Addiction Treatment Organizations

Publicly funded addiction treatment organizations have been slow to adopt pharmacotherapies. This study identifies organization-level facilitators and barriers to the use of medications in publicly funded addiction treatment organizations. Face-to-face interviews with a sample of 318 administrators of a representative sample of publicly funded addiction treatment centers in the US. Only 23.4% of programs reported using any of the five FDA-approved pharmacotherapies for treating addiction. An additional 14.3% of programs only used medications approved for the treatment of psychiatric disorders. The odds of adoption of addiction pharmacotherapies were significantly greater in government-owned programs (OR=2.82). Programs that relied more heavily on non-Medicaid public funding tended to be less likely to adopt addiction treatment medications. Greater contact with pharmaceutical representatives was positively associated with medication adoption. Current public funding policies and lack of access to medical personnel are barriers to the adoption of medications by publicly funded addiction treatment organizations. Efforts to promote adoption may also benefit from greater detailing activities by pharmaceutical representatives. These findings suggest that the large research investment devoted to developing addiction treatment medications may have limited public health impact due to the characteristics of publicly funded service delivery system as well as the limited attention given to this system by commercial purveyors of medications. Oser CB. Facilitating factors and barriers to the use of medications in publicly funded addiction treatment organizations. *J Addict Med.* 2010; 4 (2): 99-107.

Multisystemic Therapy and an Organizational Intervention for Delinquent youth: A 2 X 2 Design

This study is a randomized trial assessing the effectiveness of a 2-level strategy for implementing evidence-based mental health treatments for delinquent youth referred to juvenile court. The paper provides support for the use of interventions that address organizational and community barriers to the implementation of mental health services and evidence-based treatment programs. The study used a 2 x 2 design encompassing 14 rural Appalachian counties included 2 factors: (a) the random assignment of delinquent youth within each county to a multisystemic therapy (MST) program or usual services and (b) the random assignment of counties to the ARC (an organizational intervention standing for Availability, Responsiveness, and Continuity) for implementing effective community-based mental health services. The ARC intervention model addresses the challenges to implementing effective mental health services by providing organizational tools (e.g., teamwork, goal setting,

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feedback systems) required for identifying and addressing service barriers. The design created 4 treatment conditions (MST plus ARC, MST only, ARC only, control). The sample was 615 youth referred to juvenile court: 69% male, 91% Caucasian, and aged 9-17 years. The youth were all Medicaid eligible, had behavioral or psychiatric symptoms, and were at risk for out of home placement. Outcome measures were the Child Behavior Checklist and out-of-home placements. A multi-level mixed-effects, regression analysis of 6-month treatment outcomes found that youth total problem behavior in the MST plus ARC condition was significantly lower than in other conditions. Total problem behavior was equivalent and at nonclinical levels in all conditions by the 18-month follow-up, but youth in the MST plus ARC condition entered out-of-home placements at a significantly lower rate (16%) than youth in the control condition (34%). Two-level strategies that combine an organizational intervention such as ARC and an evidence-based treatment such as MST are promising approaches to implementing effective community-based mental health services. More research is needed to understand how such strategies can be used effectively in a variety of organizational contexts and with other types of evidence-based treatments. Glisson C, Schoenwald S, Hemmelgarn A, Green P, Dukes D, Armstrong K, Chapman J. Randomized trial of mst and arc in a two-level evidence-based treatment implementation strategy. *J Consult Clin Psychol.* 2010; 78 (4): 537-550.

Low Rates of Smoking Cessation Services Offered in Addiction Treatment Settings

Despite high rates of smoking and other tobacco use among drug-dependent individuals, adoption of smoking cessation services is not widespread in specialty addiction care settings. Through telephone interviews with clinical staff in 897 addiction treatment programs in 2007, this study documented the prevalence of smoking cessation services and major barriers to their adoption. A major barrier to implementation of smoking cessation services was the high rate of tobacco use among clinical staff (22% overall). Adoption of these services was significantly more common in larger ($p < .001$), hospital-based ($p < .001$), residential ($p < .01$) and public sector treatment programs ($p < .01$). In multivariate models controlling for organizational characteristics, significant barriers to adoption of smoking cessation services included staff beliefs that addressing smoking is a low priority (relative risk ratio [RRR] = .79, $p < .01$); lack of staff training on smoking cessation counseling (RRR = .78, $p < .01$); and reports that the demands of the addiction treatment protocol leave no time to address smoking (RRR = .74, $p < .01$). The authors suggest that greater staff training, including addressing the persistent myth that smoking cessation undermines addiction recovery, is needed in order to support the effective implementation of tobacco-related services for drug dependent treatment-seekers who smoke. Knudsen HK, Studts JL, Boyd S, Roman PM. Structural and cultural barriers to the adoption of smoking cessation services in addiction treatment organizations. 2010: *J Addict Dis.* 29(3): 294-305.

Measuring Turnover Among Substance Abuse Counselors

Staff turnover is a recognized problem in the addiction treatment field, but is difficult to quantify. Annual turnover rates between 19%-50% of staff have been reported, but these are all based on administrator estimates. This study tracked the actual turnover of a cohort of counselors and clinical supervisors in 27 addiction treatment programs over a one-year interval. A list of all clinical staff was obtained at the initial wave of a larger study; one year later, human resource managers in each program consulted records to determine whether each individual remained employed, and whether turnover was voluntary (quit) or involuntary (termination, layoff). Turnover within this cohort was 33.2% for counselors and 23.4% for clinical supervisors during the study interval. The majority of departures were due to voluntary turnover. With advance

permission from subjects, those who left were interviewed by telephone to ascertain circumstances leading to their departure. Specific reasons for turnover were largely consistent across the two groups, with the most common reason being a new job or new opportunity. More concerted retention efforts for both line staff and supervisors are warranted. Eby L, Burk H, Maher C. How serious of a problem is staff turnover in substance abuse treatment? A longitudinal study of actual turnover. *J Subst Abuse Treat.* 2010; 39 (3): 264-271.

An Effective HIV Risk-reduction Protocol for Drug-using Female Sex Workers

Female sex workers are especially vulnerable to HIV infection, particularly those who use drugs and engage in street-based sex exchange. This study examines the risk behaviors and HIV sero-status of 806 drug-using female sex workers in Miami and assesses the relative impact of two HIV and hepatitis prevention interventions on changes in risk behavior. Drug-using sex workers were recruited using targeted sampling strategies and were randomly assigned to the NIDA Standard Intervention or an innovative Sex Worker Focused (SWF) Intervention. Outcome analyses indicate that both groups benefited from participation in the intervention trial. However, the SWF Intervention was found to be more efficacious in regard to reductions in unprotected oral sex and sexual violence. Surratt H, Inciardi J. An effective HIV risk-reduction protocol for drug-using female sex workers. *J Prev Interv Community.* 2010; 38 (2): 118-131.

A Clinical Trial Evaluating Two Outpatient Interventions for Adolescent Addiction Treatment

This study evaluated the effectiveness and cost-effectiveness of two types of outpatient treatment with and without Assertive Continuing Care (ACC) for 320 adolescents with substance use disorders. The average study participant age was 15.9 years old: Seventy-six percent were male, 73% were Caucasian, 13% were African American, 93% were in school, and 73% were involved in the criminal justice system. Participants were randomly assigned to one of four conditions: (a) Chestnut's Bloomington Outpatient Treatment (CBOP) without ACC; (b) CBOP with ACC; (c) Motivational Enhancement Therapy/Cognitive Behavior Therapy-7 session model (MET/CBT7) without ACC; and (d) MET/CBT7 with ACC. All study conditions attained high rates of participant engagement and retention. Follow-up interviews were completed with over 90% of the adolescents at three, six, nine, and 12 months after treatment admission. All four conditions were associated with increased abstinence and reduced substance use problems. There was a significant time by condition effect over 12 months, with CBOP having a slight advantage for average percentage of days abstinent. Unlike previous findings that ACC provided incremental effectiveness following residential treatment, there were no statistically significant findings with regard to the incremental effectiveness of ACC following outpatient treatment. Analysis of the costs of each intervention combined with its outcomes revealed that the most cost-effective condition was MET/CBT7 without ACC. Godley S, Garner B, Passetti L, Funk R, Dennis M, Godley M. Adolescent outpatient treatment and continuing care: Main findings from a randomized clinical trial. *Drug Alcohol Depend.* 2010; 110 (1-2): 44-54.

Importance of Measuring Model Specific Adherence in the Evaluation of Evidence-based Family Therapy Models

The study examined the effectiveness of Functional Family Therapy (FFT), as compared to probation services, in a community juvenile justice setting 12 months post-treatment. The study also provides specific insight into the

interactive effects of therapist model specific adherence and measures of youth risk and protective factors on behavioral outcomes for a diverse group of adolescents. Juvenile offenders who had been remanded for probation services were randomly assigned to receive either FFT or usual probation services. The primary dependent variable was adjudicated felony recidivism occurring during the 12 months postFFT. The project involved 38 therapists and 917 families in 14 different counties that represented both rural and urban settings.

Adolescents (ages were 13 to 17 years) entered this study because they had been adjudicated for a crime and sentenced to probation: 79% were male, 78% were white, and 10% were African American. Most of the adolescents (85.4%) were drug involved, many reported alcohol use/abuse and other mental health or behavioral problems, and most of the participants had committed felony crimes. The findings suggest that FFT was effective in reducing youth behavioral problems, although only when the therapists adhered to the treatment model. High-adherent therapists delivering FFT had a statistically significant reduction of felony (35%), violent crime, and misdemeanor recidivisms(21%) , as compared to the control condition. The results represent a significant reduction in serious crimes 1 year after treatment, when delivered by a model adherent therapist. The low-adherent therapists were significantly higher than the control group in recidivism rates. There was an interaction effect between youth risk level and therapist adherence demonstrating that the most difficult families (those with high peer and family risk) had a higher likelihood of successful outcomes when their therapist demonstrated model-specific adherence. Sexton T, Turner C. The effectiveness of functional family therapy for youth with behavioral problems in a community practice setting. *J Fam Psychol.* 2010; 24 (3): 339-348.

Physician Introduction of Opioids for Pain Treatment Among Patients with Opioid Dependence and Depression

This study determined the frequency of reporting being introduced to opioids by a physician among opioid-dependent patients. Cross-sectional analyses were performed using baseline data from a cohort of opioid addicts seeking treatment with buprenorphine aged 18-65 and recruited through advertising, physician referrals, and word of mouth, and not taking medication for depression. The primary outcome was a response to the question: "Who introduced you to opiates?" Covariates included socio-demographics, depression, pain, and current and prior substance use. Of 140 participants, 29% reported that they had been introduced to opioids by a physician. Of those who were introduced to opioids by a physician, all indicated that they had initially used opioids for pain, versus only 11% of those who did not report being introduced to opioids by a physician ($p < .01$). There was no difference in current pain (78% vs. 85%, $p = .29$); however, participants who were introduced to opioids by a physician were more likely to have chronic pain (63% vs. 43%, $p = .04$). A substantial proportion of individuals with opioid dependence seeking treatment may have been introduced to opioids by a physician. Stein MD. Physician introduction to opioids for pain among patients with opioid dependence and depressive symptoms. *J Subst Abuse Treat.* 2010; 39: 378-383.

Twelve Weeks of Buprenorphine/Naloxone May Be Cost-Effective Compared with Brief Buprenorphine Detoxification for Opiate-Dependent Adolescents and Young Adults

152 opiate-dependent patients age 15-21 years at six community outpatient treatment programs in New Mexico, North Carolina, Maryland, Maine, and Pennsylvania were randomized to 12 weeks of buprenorphine/naloxone (BUP) or a 14-day taper (DETOX) as part of the NIDA Clinical Trials Network Buprenorphine/Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/ Young Adults Trial (NIDA-CTN-0010). Subjects in the BUP group

received a dose of up to 24 mg/day for 9 weeks and were tapered to zero by the end of week 12. Subjects in the DETOX group received up to 14 mg/day and were tapered to zero by day 14. All patients were also offered individual and group counseling. Urine test results, which were collected during weeks 1-12 and at 6, 9, and 12 months, were converted to opioid-free years. Quality-adjusted life years were assessed at weeks 4, 8, and 12 and months 6, 9, and 12 using the EQ-5D. Costs were estimated at the treatment program, medical insurer, and societal levels. Pharmaceutical costs were based on wholesale prices, and costs of therapy were estimated from service-level costing surveys of the participating programs. Medical service use, and other cost components such as travel time to therapy sessions, school attendance, work-force participation, and criminal justice behavior were derived from subject self-report at weeks 4 and 8 and 12 and months 6, 9, and 12. Costs associated with non-study related medical service use were based on reimbursements and out-of-pocket costs of adolescents and young adults with addictive disorders observed in the MEDSTAT MarketScan database. School attendance was valued based on rates-of-return to schooling in terms of life-time earning, employment at the wage rates reported by participants, and the dollar cost of criminal activity on findings in the literature. Missing-ness was considerable - 24.7% for non-study medical service use, 40.4% for criminal activity, 39.1% for quality of life, and 47.6% for opioid-free urines - and was addressed using inverse probability weighting. Standard errors were estimated using non-parametric bootstrap methods and used to generate acceptability curves. Results varied somewhat by perspective. BUP cost providers approximately \$1,514 more than DETOX per treatment episode in 2006 US dollars ($p < 0.001$), which translates into \$25,049 per additional QALY (with no more than an 86% chance of being cost-effective at up to a \$250,000 willingness-to-pay threshold) and \$5,610 per additional opioid-free year ($p < 0.001$) assessed at year 1. For medical insurers, who benefitted from substantial savings on health care costs for those randomized to BUP, BUP cost \$1,376/QALY (with only an 86% chance of being cost-effective) and \$308/opioid-free year ($p < 0.001$). The point estimate of \$31,264 per patient suggests that societal cost savings from BUP may be substantial, but the difference between groups was not significant at conventional levels in part due to the large variance estimated for crime costs which, although the largest savings component at \$26,224, were a reflection of infrequently reported high-cost crimes. Polsky D, Glick H, Yang J, Subramaniam G, Poole S, Woody G. Cost-effectiveness of extended Buprenorphine-Naloxone treatment for opioid-dependent youth: Data from a randomized trial. *Addiction*. 2010; 105 (9): 1616-1624.

Counselors in Recovery Report Greater Professional Commitment

A significant proportion of counselors in the specialty addiction treatment system are in recovery from their own drug or alcohol dependence. This status is often associated with a lower willingness or capacity to deliver evidence-based care, but may be associated with lower turnover and greater occupational commitment. This study surveyed 739 counselors in 27 treatment programs throughout the U.S. In regression analyses controlling for age, certification status, and education, counselors' recovery status emerged as a significant predictor of professional commitment (i.e., commitment to a counseling career, $p < .01$) but not of organizational commitment (i.e., commitment to remain with their current treatment organization, $p < .10$). The authors suggest that because professional commitment is likely to have beneficial downstream results for quality of care, treatment programs should implement strategies for enhancing professional commitment among all clinical staff. Curtis, SL, Eby LT. Recovery at work: The relationship between social identity and commitment among substance abuse counselors. *J Subst Abuse Treat*. 2010; 39 (3): 248-254.

Bipolar Individuals with Co-morbid Alcohol Use Disorder at

Elevated Risk for Suicide Attempts

Bipolar disorder is associated with a high rate of suicide attempt, and alcohol use disorders have also been associated with elevated risk for suicidal behavior. Whether risk for suicidal behavior is elevated when these conditions are co-morbid has not been addressed in epidemiologic studies. In this study 1,643 individuals with a DSM-IV lifetime diagnosis of bipolar disorder were identified from 43,093 general-population respondents who were interviewed in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions. Assessments were made using the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV). Lifetime prevalence of reported history of suicide attempt and suicidal thoughts among bipolar disorder respondents with and without DSM-IV lifetime alcohol use disorders (abuse or dependence) was assessed using chi square and adjusted odds ratios with confidence intervals. Logistic regression was used to test the relevance of other co-morbid clinical conditions to suicide risk in bipolar respondents with and without co-morbid alcohol use disorders. More than half of the respondents (54%) who met criteria for bipolar disorder also reported alcohol use disorder. Bipolar individuals with co-morbid alcohol use disorder were at greater risk for suicide attempt than those individuals without alcohol use disorder (adjusted odds ratio=2.25; 95% CI, 1.61-3.14) and were more likely to have co-morbid nicotine dependence and drug use disorders. Nicotine dependence and drug use disorders did not increase risk for suicidal behavior among those with bipolar disorder, nor did they confer additional risk among bipolar respondents who also reported alcohol use disorder. Despite greater psychopathological burden, individuals with co-morbid bipolar disorder and alcohol use disorder did not receive more treatment or more intensive treatment. The data suggest that suicidal behavior is more likely to occur in bipolar respondents who also suffer from alcohol use disorder. Interventions to reduce suicide risk in bipolar disorder need to address the common and high-risk co-morbidity with alcohol use disorders. Oquendo M, Currier D, Liu S, Hasin D, Grant B, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: Results from the National Epidemiologic Survey On Alcohol And Related Conditions (NESARC). *J Clin Psychiatry*. 2010; 71 (7): 902-909.

Erectile Dysfunction in Opioid Users: Lack of Association with Serum Testosterone

This study describes the prevalence of erectile dysfunction (ED) among 57 men, using illicit opioids who presented to a primary care program for buprenorphine therapy. Participants' mean age was 40 years and 34% reported ED. Low total testosterone was detected in 17% of those reporting ED, but total testosterone was not significantly associated with ED. Examining multiple co-morbidities and laboratory parameters, only older age was significantly associated with ED ($r = .27, P < .05$). ED is highly prevalent among men abusing opioids, but low total testosterone is rarely the cause. Cioe P, Friedmann P, Stein M, Stein M. Erectile Dysfunction in opioid users: Lack of association with serum testosterone. *J Addict Dis*. 2010; 29 (4): 455-460.

Codifying Therapist Behaviors Supportive of African American Families in Family-Based Addiction Treatment

Identifying psychotherapy processes that likely contribute to client outcome with ethnic minorities is a vital practice and research need, particularly within family-focused, evidence-based treatments (EBT) for youth with externalizing problems. Identifying process variables within a cross-cultural context may improve the efficacy of EBTS by informing psychotherapists how to modify their behavior when working with ethnically diverse clients. The authors described

one approach to the development of culturally competent psychotherapy, using an observational coding system comprising Afro-centric codes to investigate culturally relevant therapist behaviors. The research team conducted structured interviews with African American and Caucasian therapists and supervisors who had between 2 and 10 years of experience. Interviewers queried respondents about therapist behaviors they believed contributed to treatment success and failure with families. Following these interviews, clinical researchers independently read all of the interview transcripts and identified positive and negative therapist behaviors. This yielded a broad range of therapist behaviors believed to be helpful or unhelpful, specifically with African American families, and with families in general, and the resultant positive and negative behaviors were consolidated. Qualitative examples illustrated the quantitative findings relating to therapist in-session behavior that promote client engagement and positive responding during therapy. Findings suggest a variety of therapist behaviors that may enhance family engagement during the most demanding phase of treatment. Focusing on strengths and supporting specific positive changes (reinforce) are practitioner behaviors that were found to be useful in treatment, regardless of the race, racial match between therapist and caregiver, and socioeconomic status of the caregiver. Cunningham P, Foster S, Warner S. Culturally relevant family-based treatment for adolescent delinquency and substance abuse: Understanding within-session processes. *J Clin Psychol.* 2010; 66 (8): 830-846.

Stress Potentiates Conditioned Cue-Induced Reinstatement of Heroin-Seeking in Rats: Translational Implications For Relapse Prevention and Treatment

One particularly salient feature that occurs during abstinence from drug use is the ability of drug-associated environmental cues (e.g., drug paraphernalia) to elicit drug craving and subsequent relapse. Stress can also trigger craving and relapse in abstinent drug-dependent individuals. Although the role of these two critical factors in relapse has been extensively studied, the interaction between stress and drug-associated cues in relapse has been less well characterized. Using an animal model of relapse, we assessed the effects of the pharmacological stressor, yohimbine (1.25 or 2.5mg/kg), on reinstatement of extinguished heroin-seeking in rats either in the presence or absence of heroin-associated cues. Yohimbine, in the absence of heroin-associated cues, and cues by themselves reliably reinstated heroin-seeking over extinction levels. Notably, animals showed significantly potentiated responding when yohimbine preceded cue-induced reinstatement (3-4x higher over cues or yohimbine alone). These results demonstrate that exposure to heroin-paired cues during yohimbine-induced stress greatly potentiates heroin-seeking. These findings have important clinical implications for relapse prevention and treatment efforts, as relapse to drug use in humans is precipitated by a combination of factors that often involve stress and conditioned drug cues. The current findings, coupled with previous research, support the simultaneous targeting of both stress and cue activation during relapse intervention. Banna K, Back S, Do P, See R. Yohimbine stress potentiates conditioned cue-induced reinstatement of heroin-seeking in rats. *Behav Brain Res.* 2010; 208 (1): 144-148.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - CTN-Related Research

Impact of Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment on Smoking Cessation Intervention in ADHD Smokers: A Randomized, Double-Blind, Placebo-Controlled Trial

High smoking rates in adults with attention-deficit/hyperactivity disorder (ADHD) and nicotine's amelioration of ADHD suggest that effective ADHD treatment might facilitate smoking cessation. This study evaluated if using osmotic-release oral system methylphenidate (OROS-MPH) to treat ADHD enhances response to smoking cessation treatment in adult ADHD smokers. A randomized, double-blind, placebo-controlled, 11-week trial with a 1-month follow-up was conducted at 6 clinical sites between December 2005 and January 2008. Adults (aged 18-55 years) meeting DSM-IV criteria for ADHD, interested in quitting smoking, were randomly assigned to OROS-MPH titrated to 72 mg/d (n = 127) or placebo (n = 128). Participants received brief, weekly, individual smoking cessation counseling for 11 weeks and 21 mg/d nicotine patches starting on the smoking quit day (day 27) through study week 11. Of 255 randomly assigned participants, 204 (80%) completed the trial. Prolonged abstinence rates, 43.3% and 42.2%, for the OROS-MPH and placebo groups, respectively, did not differ significantly (OR = 1.1; 95% CI, 0.63-1.79; P = .81). Relative to placebo, OROS-MPH evidenced a greater reduction in DSM-IV ADHD Rating Scale score (P < .0001) and in cigarettes per day during the post-quit phase (P = .016). Relative to placebo, OROS-MPH increased blood pressure and heart rate to a statistically, but not clinically, significant degree (P < .05); medication discontinuation did not differ significantly between treatments. Treatment for ADHD did not improve smoking cessation success; OROS-MPH, relative to placebo, effectively treated ADHD and was safe and generally well tolerated in this healthy sample of adult ADHD smokers. Winhusen TM, Somoza EC, Brigham GS, Liu DS, Green CA, Covey LS, Croghan IT, Adler LA, Weiss RD, Leimberger JD, Lewis DF, Dorer EM. Impact of attention-deficit/hyperactivity disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2010 May 18. [Epub ahead of print].

Principles for Defining Adverse Events in Behavioral Intervention Research: Lessons From A Family-Focused Adolescent Drug Abuse Trial

Behavioral intervention research has lagged behind biomedical research in developing principles for defining, reporting, and monitoring adverse events (AEs) and unanticipated problems. Principles for defining AEs and their application in a large national multi-site family therapy study for substance-using adolescents, The Brief Strategic Family Therapy (BSFT) Effectiveness Study are presented. The BSFT Effectiveness study tested how BSFT compares

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to Treatment as Usual (TAU) for the treatment of drug-abusing adolescents. During protocol development, experts in the BSFT intervention defined the procedures for identifying, tracking and reporting AEs for drug using adolescents and their family members. The team identified five key guiding principles: 1) AEs should be validated, 2) AEs should be plausible, 3) monitoring systems should assess relatedness, 4) monitoring systems should be systematic, and 5) monitoring systems are a shared responsibility. The following non-serious AEs were identified: arrest, school suspension and drop out, runaway, kicked out of home and violence. The serious AEs for the identified adolescent participant and all other consented family members were physical or sexual abuse, suicidal behavior, homicidal behavior, hospitalization (drug related or psychiatric related only) and death. More than 50% of the adolescent population (277/481 = 57.5 %) experienced an AE during the trial. Family members experienced less AEs, (61/1338 = 4.5%). The most common AE for the adolescent group was arrest (164/277= 59.2%), followed by school suspension/dropout (143/277 = 51.6%), and runaway (79/277= 28.5 %). For the family member group, the most common AE was violence (25/ 61 = 40.9%) followed by arrest (13/61 = 21.3%). There was a significant difference in the presence of AEs in family members that were randomized to BSFT 44/721 (6.1%) when compared to TAU 17/617 (2.8%) ($p = 0.004$). A probable explanation for this is that there were more opportunities to identify AEs for family members assigned to BSFT because family members attended therapy sessions. This difference may also represent the risk for family members that participate in an evidence-based family intervention like BSFT. The strategies and principles may be useful for future safety plan development and assessment in behavioral family intervention research. Horigian VE, Robbins MS, Dominguez R, Ucha J, Rosa CL. Principles for defining adverse events in behavioral intervention research: lessons from a family-focused adolescent drug abuse trial. *Clin Trials*. 2010; 7(1): 58-68.

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Teaching Condom Use Skills: Practice is Superior to Observation

Men exposed to a condom skills practice exercise were thought to perform better on condom skills measures than those exposed to a demonstration only or to no intervention. To prove this hypothesis and as part of a larger National Institute on Drug Abuse (NIDA) Clinical Trials Network HIV Prevention protocol, men in substance abuse treatment were administered male and female condom use skills measures (MCUS, FCUS) at pre-intervention, 2 weeks, 3 months, and 6 months post-intervention. The MCUS and FCUS scores were compared for 3 intervention exposure groups (demonstration only [DO, $n = 149$], demonstration plus practice [D+P; $n = 112$], attended no sessions [NS, $n = 139$]) across 4 assessment time points using a mixed effects linear regression model. A statistically significant intervention group-by-time effect ($P < .0001$) was found for both the MCUS and FCUS. Post hoc, pairwise linear trends across time indicated that for both the MCUS and the FCUS, the D+P group was significantly superior to the DO group and the NS group. Calsyn DA, Hatch-Maillette MA, Doyle SR, Cousins S, Chen T, Godinez M. Teaching condom use skills: practice is superior to observation. *Subst Abus*. 2010 Oct; 31(4): 231-239.

Effect of Job Skills Training on Employment and Job Seeking Behaviors in an American Indian Substance Abuse Treatment Sample

Employment difficulties are common among American Indian individuals in substance abuse treatment. To address this problem, the Southwest Node of NIDA's Clinical Trials Network conducted a single-site adaptation of its national Job Seekers Workshop study in an American Indian treatment program, Na'Nizhoozhi Center (NCI). 102 (80% men, 100% American Indian)

participants who were in residential treatment and currently unemployed were randomized to (1) a three session, manualized program (Job seekers workshop: JSW) or (2) a 40-minute video on how to interview for a job (Job Interviewing Video: JIV). Outcomes were assessed at 3-month follow up: 1) number of days to a new taxed job or enrollment in a job-training program, and 2) total hours working or enrolled in a job-training program. No significant differences were found between the two groups for time to a new taxed job or enrollment in a job-training program. There were no significant differences between groups in substance use frequency at 3-month follow-up. These results do not support the use of the costly and time-consuming JSW intervention in this population and setting. Despite of the lack of a demonstrable treatment effect, this study established the feasibility of including a rural American Indian site in a rigorous CTN trial through a community-based participatory research approach. Foley K, Pallas D, Forcehimes AA, Houck JM, Bogenschutz MP, Keyser-Marcus L, Svikis D. Effect of job skills training on employment and job seeking behaviors in an American Indian substance abuse treatment sample. *J Voc Rehab.* 2010 Oct; 33(3): 181-192.

Gender and Racial/Ethnic Differences in Addiction Severity, HIV Risk, and Quality of Life Among Adults in Opioid Detoxification: Results from the National Drug Abuse Treatment Clinical Trials Network

There is limited information concerning individuals seeking detoxification, and the opportunity to engage patients in aftercare to prevent relapse is often missed. Clinical profiles of a geographically diverse sample of 343 opioid-dependent adults in 12 treatment programs were examined to discern the needs of a growing number of women and whites with opioid addiction and to inform interventions aimed at improving use of aftercare or rehabilitation. Results from these two National Institute on Drug Abuse (NIDA) Clinical Trials Network multisite studies (CTN001-002) indicated that women and whites were more likely than men and African Americans to have greater psychiatric and family/social relationship problems and report poorer health-related quality of life and functioning. Whites and Hispanics exhibited higher levels of total HIV risk scores and risky injection drug use scores than African Americans, and Hispanics showed a higher level of unprotected sexual behaviors than whites. African Americans were more likely than whites to use heroin and cocaine and to have more severe alcohol and employment problems. Findings highlight the need to develop effective combined psychosocial and pharmacologic treatments to meet the diverse needs of women and white opioid-abusing population. Elevated levels of HIV risk behaviors among Hispanics and whites also warrant more research to delineate mechanisms and to reduce their risky behaviors. Wu LT, Ling W, Burchett B, Blazer DG, Shostak J, Woody GE. Gender and racial/ethnic differences in addiction severity, HIV risk, and quality of life among opioid-dependent patients: Results from the Clinical Trials Network. *Subst Abuse and Rehab.* 2010 Dec; 1: 13-22.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - International Research

HHH Fellow: David Otiashvili, Georgia, 2003-2004

WHO/NIDA/CPDD International Traveling Fellow: Irma Kirtadze, Georgia, 2010

Meyer W, Costenbader EC, Zule WA, Otiashvili D, Kirtadze I. 'We are ordinary men': MSM identity categories in Tbilisi, Georgia. *Culture, Health & Sexuality*. 2010 Nov; 12 (8): 955-971.

Men who have sex with men remain largely absent from the health statistics of many Eastern European countries. This relative dearth compared to other parts of the world may be attributed to the generally hidden nature of this population. The tendency to employ Western sexual identity labels, rather than locally meaningful categories of identity, may also make it difficult to identify men who have sex with other men. In a pilot study of HIV risk in Tbilisi (Georgia), we used a suite of qualitative techniques - focus groups, individual semi-structured interviews and pile-sort exercises - to probe the opinions, knowledge and experiences of 65 Georgian men. The authors identified locally meaningful men-who-have-sex-with-men types, demonstrating a complex intersectionality of sexual preference, socio-economic status, behavior and geography. Positioning within these types appeared to impact a man's exposure to the social stigma of homosexuality; the sexual, physical and mental health risks that he faced; and his access to treatment and counseling. Results suggest the use of imported identity categories limits researchers' ability to identify men who have sex with other men in Georgia and that further research aimed at elucidating locally meaningful categories is needed - research likely to lead to more-effective group interventions and facilitate a better understanding of holistic individual health needs.

HHH Fellow: Tomas Zabransky, Czech Republic, 2003-2004

Mravčík V, Zábanský T, Vorel F. Ethanol and other psychoactive substances in fatal road traffic accidents in the Czech Republic in 2008. *Casopis Lekarů Ceskych*. 2010; 149(7): 332-336.

The purpose of this research was to map the recent prevalence of alcohol and other psychoactive substances in deceased victims of traffic accidents in the Czech Republic. The studied sample consisted of individuals autopsied in the departments of forensic medicine who died during traffic accidents in 2008 and were toxicologically tested for one or more of the following substances: ethanol, volatile substances, cannabis, opiates, stimulants, cocaine, benzodiazepines, and barbiturates. Case definition involved alcohol cases with blood alcohol concentration (BAC) 0.2 g/kg and higher; with cannabis, detections of active THC metabolites only were taken into account; from cases where volatile substances (solvents) were detected we included into the positive cases only those where substances were not produced post mortem or in some physiological or pathological statuses. The sample consisted of 1,040 persons deceased in traffic accidents, of whom 582 (56.0%) were toxicologically tested for one or more of the substances listed above. The

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sample has been divided into two subsamples--one of 778 (74.8%) active participants of road traffic accidents (pedestrians, bicyclists, and drivers) and other subsample consisting of 262 (25.4%) non-active participants. Ethanol was found in 38.3% of 381 tested and at least one of other psychoactive substances was found in 11.7% of 384 tested active participants--of those, stimulants (mostly methamphetamine) were found most frequently (6.5% of 337 tested), cannabis (5.9% of 203 tested) and benzodiazepines (3.9% of 363 tested active participants). Drivers were positive for ethanol in 29.2% cases, for one or more of other psychoactive substances except ethanol in 12.7% cases, most frequently for stimulants (9.2%) and cannabis (6.2%). Professional drivers were found negative for ethanol and other psychoactive substance except of one case of methamphetamine (6.7%). The study confirms high prevalence of alcohol and other psychoactive substances, especially stimulants (methamphetamine), cannabis and benzodiazepines, among deceased participants of road traffic accidents including drivers in the Czech Republic.

HHH Fellow: Olga Toussova, Russia, 2001-2002

Abdala N, White E, Toussova OV, Krasnoselskikh TV, Verevchkin S, Kozlov AP, Heimer R. Comparing sexual risks and patterns of alcohol and drug use between injection drug users (IDUs) and non-IDUs who report sexual partnerships with IDUs in St. Petersburg, Russia. *BMC Public Health*. 2010 Nov 5;10: 676.

To date, the great majority of Russian HIV infections have been diagnosed among IDUs and concerns about the potential for a sexual transmission of HIV beyond the IDU population have increased. This study investigated differences in the prevalence of sexual risk behaviors between IDUs and non-IDUs in St. Petersburg, Russia and assessed associations between substance use patterns and sexual risks within and between those two groups. Cross-sectional survey data and biological test results from 331 IDUs and 65 non-IDUs who have IDU sex partners were analyzed. Multivariate regression was employed to calculate measures of associations. IDUs were less likely than non-IDUs to report multiple sexual partners and unprotected sex with casual partners. The quantity, frequency and intensity of alcohol use did not differ between IDUs and non-IDUs, but non-IDUs were more likely to engage in alcohol use categorized as risky per the alcohol use disorders identification test (AUDIT-C). Risky sexual practices were independently associated with monthly methamphetamine injection among IDUs and with risky alcohol use among non-IDUs. Having sex when high on alcohol or drugs was associated with unprotected sex only among IDUs. Greater prevalence of sexual risk among non-IDUs who have IDU sex partners compared to IDUs suggests the potential for sexual transmission of HIV from the high-prevalence IDU population into the general population. HIV prevention programs among IDUs in St. Petersburg owe special attention to risky alcohol use among non-IDUs who have IDU sex partners and the propensity of IDUs to have sex when high on alcohol or drugs and forgo condoms.

Niccolai LM, Verevchkin SV, Toussova OV, White E, Barbour R, Kozlov AP, Heimer R.

Estimates of HIV incidence among drug users in St. Petersburg, Russia: continued growth of a rapidly expanding epidemic. *European Journal of Public Health*. 2010 Aug 26. [Epub ahead of print]

Russia has one of the world's fastest growing HIV epidemics and it has been largely concentrated among injection drug users (IDU). St Petersburg, Russia's second largest city, is one of the country's regions that has been most affected by the HIV epidemic. To monitor the current epidemic situation, the authors sought to estimate recent HIV incidence among IDUs in St Petersburg. In a cross-sectional study of 691 IDU recruited during 2005-08, HIV incidence was estimated by two methods: a retrospective cohort analysis and BED capture enzyme immunoassay (EIA) results. Socio-demographic and behavioural correlates of incident infections and spatial patterns were examined. In the

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retrospective cohort analysis, the incidence rate was estimated to be 14.1/100 person-years [95% confidence interval (CI) 10.7-17.6]. Using results of BED EIA and two correction formulas for known misclassification, incidence estimates were 23.9 (95% CI 17.8-30.1) and 25.5 (95% CI 18.9-32.0) per 100 person-years. Independent correlates of being recently infected included current unemployment ($P = 0.004$) and not having injected drugs in the past 30 days ($P = 0.03$). HIV incident cases were detected in all but one district in the city, with focal areas of transmission observed to be expanding. High HIV incidence among IDU in St Petersburg attests to continued growth of the epidemic. The need for expansion of HIV prevention interventions targeted to vulnerable populations throughout the city is urgent. These results also suggest that the BED EIA may over-estimate incidence even after correction for low specificity.

Grau LE, White E, Niccolai LM, Toussova OV, Verevochkin SV, Kozlov AP, Heimer R.

HIV Disclosure, Condom Use, and Awareness of HIV Infection Among HIV-Positive, Heterosexual Drug Injectors in St. Petersburg, Russian Federation. *AIDS and Behavior*. 2010 Aug 11. [Epub ahead of print]

The authors examined the prevalence of HIV disclosure to sexual partners by HIV-positive drug injectors (IDUs) in St. Petersburg, Russia and compared the magnitude and direction of associations of condom use with awareness of one's HIV infection and disclosure to partners. Among 157 HIV-infected participants, awareness of infection at time of last intercourse was associated with condom use with partners perceived to be HIV-negative (aOR 6.68, 95% CI 1.60-27.88). Among the 70 participants aware of their infection prior to enrollment, disclosure to potentially uninfected sexual partners was independently and negatively associated with condom use (aOR 0.13, 95% CI 0.02-0.66).

Disclosure was independently associated with having injected ≥ 9 years (aOR 6.04, 95% CI 1.53-23.77) and partnership with another IDU (aOR 3.61, 95% CI 1.44-9.06) or HIV-seropositive (aOR 45.12, 95% CI 2.79-730.46). Scaling up HIV testing services and interventions that increase the likelihood of individuals receiving their test results is recommended.

Masharsky AE, Dukhovlinova EN, Verevochkin SV, Toussova OV, Skochilov RV, Anderson JA, Hoffman I, Cohen MS, Swanstrom R, Kozlov AP.

A substantial transmission bottleneck among newly and recently HIV-1-infected injection drug users in St Petersburg, Russia. *Journal of Infectious Diseases*. 2010 Jun 1; 201(11):1697-1702.

There are limited data on the genetic complexity of human immunodeficiency virus type 1 (HIV-1) after transmission among a cohort of injection drug users (IDUs). The authors used single-genome amplification of HIV-1 env to determine the genotypic characteristics of virus among IDUs with acute infection in St Petersburg, Russia. Their results indicate that a single variant was transmitted in a majority of cases (9 of 13 participants), which is analogous to what is observed in sexual transmission. These data are most consistent with a genetic bottleneck during transmission by injection drug use that is due to a small inoculum, which most often results in the transmission of a low-complexity viral population.

HHH Fellow: Sandra Reid, Trinidad and Tobago, 1992-1993

Reid SD, Nielsen AL, Reddock R. Changes in HIV needs identified by the National AIDS Hotline of Trinidad and Tobago. *Revista Panamericana de Salud P blica*. 2010 Feb; 27(2): 93-102.

The objectives of this study were to examine utilization of the National AIDS Hotline of Trinidad and Tobago (AIDSLINE), evaluate its validity as a reliable data source for monitoring national HIV-related needs, and identify changes in caller requests between two different time periods. A total of 7,046 anonymous hotline calls in 1998-2002 (T1) and 2,338 calls in 2007 (T2) were analyzed for associations between caller characteristics and call content. A subsample of the data was also analyzed qualitatively. T1 findings were compared with HIV-

related data collected by national policy-makers during that period, to evaluate the hotline's validity as a data source, and findings from T2, to reveal changes in call content over time. In T1, the hotline was well utilized for information and counseling by both the general population and those living with HIV/AIDS. Call content from T2 indicated an increase versus T1 in 1) general awareness of HIV and other sexually transmitted diseases; 2) HIV testing; and 3) knowledge of HIV symptoms and transmission. HIV-related mental health needs, and the relationship between HIV and both child sexual abuse (CSA) and intimate partner violence (IPV), were identified as emerging issues. AIDSLINE is a well-utilized tool for providing information and counseling on national HIV-related issues, and a valid, cost-effective, easily accessed information source for planners and policy-makers involved in HIV management. Over the two study periods, there was an increase in HIV awareness and testing and in requests related to mental health, CSA, and IPV, but no change in sexual behaviors.

HHH (2002-2003) and INVEST/CTN (2007) Fellow: Amit Chakrabarti, India

Potter JS, Chakrabarti A, Domier CP, Hillhouse MP, Weiss RD, Ling W. Pain and continued opioid use in individuals receiving buprenorphine-naloxone for opioid detoxification: secondary analyses from the Clinical Trials Network. *Journal of Subs Abuse Treatment*. 2010 Jun; 38 Suppl 1: S80-86.

Pain complaints are common among individuals with opioid dependence. However, few studies investigate pain during opioid detoxification or the impact this pain has on continued opioid use. This secondary analysis utilized data from two Clinical Trials Network randomized controlled trials of buprenorphine-naloxone for short-term opioid detoxification to examine the extent to which pain was associated with continued opioid use during and immediately following a 13-day detoxification protocol. At follow-up, more severe pain was associated with a greater number of self-reported days of opioid use during the prior 30 days ($p < .05$) but was not associated with urine toxicology results collected at follow-up. These results, although mixed, have potentially important clinical implications for assessing and addressing pain during opioid detoxification. Pain that is experienced during and immediately following medically monitored detoxification may be associated with continued opioid use. These findings lend further support for continued research on pain among patients with opioid dependence.

HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992

HHH Fellow: Sergio Nicastrì, Brazil, 1993-1994

WHO/NIDA/CPDD International Traveling Fellow: Paulo Cunha, Brazil

Cunha PJ, Nicastrì S, de Andrade AG, Bolla KI. The frontal assessment battery (FAB) reveals neurocognitive dysfunction in substance-dependent individuals in distinct executive domains: Abstract reasoning, motor programming, and cognitive flexibility. *Addictive Behaviors*. 2010 Jun 2. [Epub ahead of print] Substance-dependence is highly associated with executive cognitive function (ECF) impairments. However, considering that it is difficult to assess ECF clinically, the aim of the present study was to examine the feasibility of a brief neuropsychological tool (the Frontal Assessment Battery - FAB) to detect specific ECF impairments in a sample of substance-dependent individuals (SDI). Sixty-two subjects participated in this study. Thirty DSM-IV-diagnosed SDI, after 2weeks of abstinence, and 32 healthy individuals (control group) were evaluated with FAB and other ECF-related tasks: digits forward (DF), digits backward (DB), Stroop Color Word Test (SCWT), and Wisconsin Card Sorting Test (WCST). SDI did not differ from the control group on sociodemographic variables or IQ. However, SDI performed below the controls in DF, DB, and FAB. The SDI were cognitively impaired in 3 of the 6 cognitive domains assessed by the FAB: abstract reasoning, motor programming, and cognitive flexibility. The FAB correlated with DF, SCWT, and WCST. In addition, some neuropsychological measures were correlated with the amount of alcohol, cannabis, and cocaine use. In conclusion, SDI performed more poorly than the comparison group on the FAB and the FAB's results were associated with other

ECF-related tasks. The results suggested a negative impact of alcohol, cannabis, and cocaine use on the ECF. The FAB may be useful in assisting professionals as an instrument to screen for ECF-related deficits in SDI.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Szobot CM, Roman T, Hutz MH, Genro JP, Shih MC, Hoexter MQ, Joenior N, Pechansky F, Bressan RA, Rohde LA. Molecular imaging genetics of methylphenidate response in ADHD and substance use comorbidity. *Synapse*. 2010 Jun 30. [Epub ahead of print]

Attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) are highly comorbid and may share a genetic vulnerability. Methylphenidate (MPH), a dopamine transporter (DAT) blocker, is an effective drug for most ADHD patients. Although dopamine D4 receptor (DRD4) and dopamine transporter (DAT1) genes have a role in both disorders, little is known about how these genes influence brain response to MPH in individuals with ADHD/SUDs. The goal of this study was to evaluate whether ADHD risk alleles at DRD4 and DAT1 genes could predict the change in striatal DAT occupancy after treatment with MPH in adolescents with ADHD/SUDs. Seventeen adolescents with ADHD/SUDs underwent a SPECT scan with [^{99m}Tc]TRODAT-1 at baseline and after 3 weeks on MPH. Caudate and putamen DAT binding potential was calculated. Comparisons on DAT changes were made according to the subjects' genotype. The combination of both DRD4 7-repeat allele (7R) and homozygosity for the DAT1 10-repeat allele (10/10) was significantly associated with a reduced DAT change after MPH treatment in right and left caudate and putamen, even adjusting the results for potential confounders (P

HHH Fellow: Sergey Dvoryak, Ukraine, 1999-2000

Booth RE, Lehman WE, Latkin CA, Dvoryak S, Brewster JT, Royer MS, Sinitsyna L. Individual and Network Interventions With Injection Drug Users in 5 Ukraine Cities. *American Journal of Public Health*. 2010 Apr 15. [Epub ahead of print]

The effects of an individual intervention versus a network intervention on HIV-related injection and sexual risk behaviors among street-recruited opiate injection drug users in 5 Ukraine cities were evaluated. Between 2004 and 2006, 722 opiate injection drug users were recruited to participate in interventions that were either individually based or based on a social network model in which peer educators intervened with their network members. Audio computer-assisted self-interview techniques were used to interview participants at baseline and follow-up. Multiple logistic analyses controlling for baseline injection and sexual risks revealed that both peer educators and network members in the network intervention reduced injection related risk behaviors significantly more than did those in the individually based intervention and that peer educators increased condom use significantly more than did those in the individual intervention. Individual intervention participants, however, showed significantly greater improvements than did network members with respect to reductions in sexual risk behaviors. The authors conclude that social network interventions may be more effective than individually based interventions in changing injection risk behaviors among both peer educators and network members. The effectiveness of network interventions in changing sexual risk behaviors is less clear, probably owing to network composition and inhibitions regarding discussing sexual risk behaviors.

HHH Fellow: Chung Tai Lee, South Korea, 1994-1995

Lee KU, Lee YM, Nam JM, Lee HK, Kweon YS, Lee CT, Jun TY. Antidepressant-Induced Sexual Dysfunction among Newer Antidepressants in a Naturalistic Setting. *Psychiatry Investigation*. 2010 Mar; 7(1): 55-59. Epub 2010 Feb 8.

Antidepressants used to treat depression are frequently associated with sexual dysfunction. Sexual side effects affect the patient's quality of life and, in long-term treatment, can lead to non-compliance and relapse. However, studies covering many antidepressants with differing mechanisms of action were

scarce. The present study assessed and compared the incidence of sexual dysfunction among different antidepressants in a naturalistic setting. Participants were married patients diagnosed with depression, per DSM-IV diagnostic criteria, who had been taking antidepressants for more than 1 month. The authors assessed the participants via the Arizona Sexual Experiences Scale (ASEX), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI), and assessed their demographic variables, types and dosages of antidepressants, and duration of antidepressant use via their medical records. One hundred and one patients (46 male, 55 female, age 42.2+/-7 years) completed the instruments. Thirteen were taking fluoxetine (mean dose 21.3+/-8.5 mg/day), 24 were taking paroxetine (mean dose 20.4+/-7.2 mg/day), 20 taking citalopram (mean dose 22.1+/-6.5 mg/day), 22, venlafaxine (mean dose 115.7+/-53.2 mg/day) and 22, mirtazapine (mean dose 18+/-8.7 mg/day). Mean ages, sex ratios, and BDI and STAI scores did not differ significantly across antidepressants. A substantial number of participants (46.5%, n=47) experienced sexual dysfunction. The prevalence of sexual dysfunction differed across drugs: citalopram 60% (n=12), venlafaxine 54.5% (n=12), paroxetine 54.2% (n=13), fluoxetine 46.2% (n=6), and mirtazapine 18.2% (n=4). Regression analyses revealed the significant factors for sexual dysfunction were being female, total scores on the BDI and SAI, and type of antidepressant ($F=4.92$, $p<0.0001$). Of the antidepressants, the mirtazapine group's total ASEX score was significantly lower than the scores of the citalopram, fluoxetine, and paroxetine groups. The incidence of sexual dysfunction was substantially high during antidepressant treatment. The incidence of sexual dysfunction differed among antidepressants having different mechanisms of action. This study suggests the need for clinicians to consider the impact of pharmacotherapy on patients' sexual functioning in the course of treatment with antidepressants.

HHH Fellow: Roumen Sedefov, Bulgaria 1994-1995

Griffiths P, Lopez D, Sedefov R, Gallegos A, Hughes B, Noor A, Royuela L. Khat use and monitoring drug use in Europe: The current situation and issues for the future.

Journal of Ethnopharmacology. 2010 May 7. [Epub ahead of print]

The aim of this study was to review the information available on the use of khat (*Catha edulis*) in the EU, and to assess the future use of this drug and related substances. Khat is not controlled by international law and it has not been systematically included in the list of illicit drugs monitored in the EU. The current principal source of information on khat use in Europe is the early-warning system set up to monitor new and emerging drugs. Further information was obtained from official national reports to the EMCDDA and from the scientific literature. Across Europe, the use of khat is low. Khat use is limited to countries with immigrant communities from countries where khat use is common (such as Ethiopia, Somalia and Kenya). Information on the prevalence of khat use in the general population is scarce. Data on seizures provide an insight on the situation, though these may be difficult to interpret. The most recent estimates suggest that Europe accounts for about 40% of the khat seized worldwide. The shortage of data on the use and patterns of use of khat in Europe does not allow an evaluation of the needs for health and social interventions in communities in which the drug is used. But seizures of the plant are increasing in the EU, and more synthetic derivatives of the pharmacologically active ingredients of the plant (cathine and cathinone) are appearing on the market. Some of these, like mephedrone, have significant potential for future diffusion, and are likely to play a greater role on the European drug scene of the future.

HHH Fellow: Alisher Latypov, Tajikistan, 2002 - 2003

Latypov A. Healers and psychiatrists: the transformation of mental health care in Tajikistan.

Transcultural Psychiatry. 2010 Jul; 47(3): 419-451.

This article examines the transformation of mental health care in Tajikistan

from the time of Russian colonization of Central Asia until the most recent years of post-independence. It incorporates a review of published literature into the analysis of locally available reports, focus group discussions, interviews and oral histories collected between 2005 and 2008. Traditional healers play a significant role in contemporary Tajikistan, where mental health care provision is influenced by the legacy of Soviet psychiatry. Tajik mental health care may now be in a "dormant" phase, characterized by a widespread neglect of people with mental illnesses.

INVEST Fellow: Min Zhao, China, 2001-2002

Yu X, Xiao D, Li B, Liu Y, Wang G, Chen J, Bai C, Pan J, Wan H, Li Q, Zhou X, Liao R, Li Q, Wang C, Chen R, Tang Y, Mo H, Zhao M, Du J, Li J, Kang L, Wang C. Evaluation of the Chinese versions of the Minnesota nicotine withdrawal scale and the questionnaire on smoking urges-brief. *Nicotine & Tobacco Research*. 2010 Jun; 12(6): 630-634. Epub 2010 May 24.

The objectives of this study were to evaluate the reliability and validity of the Chinese versions of Minnesota Nicotine Withdrawal Scale and Questionnaire on Smoking Urges-Brief (MNWS-C and QSU-Brief-C) in Chinese smokers. MNWS and QSU-Brief were translated into Chinese version through 10 steps. The reliability and validity of Chinese versions of the two scales were evaluated based on the data collected from 354 subjects. Cronbach's alpha coefficient was calculated to assess the reliability. Construct validity were evaluated with confirmatory factor analysis. Criteria validity was examined with correlation analysis between scale scores and patient-evaluated scores of craving and tobacco withdrawal symptoms. Cronbach's alpha coefficient of QSU-Brief-C was .96. Confirmatory factor analysis demonstrated that the fit indexes (adjusted goodness-of-fit index [AGFI], comparative fit index [CFI], normed fit index [NFI], and non-normed fit index [NNFI]) exceeded or approached 0.9. The correlation between QSU-Brief-C scores and patient-evaluated craving scores were statistically significant ($r = .75, p < .0001$). Cronbach's alpha coefficient of MNWS-C was .90. Confirmatory factor analysis demonstrated that the fit indexes (AGFI, CFI, NFI, and NNFI) exceeded 0.9. The correlation between MNWS-C scores and patient-evaluated discomfort scores were statistically significant ($r = .68, p < .0001$). Both QSU-Brief-C and MNWS-C have satisfactory validity and reliability and retain the two dimensions identified in their corresponding original English versions, which suggest that QSU-Brief-C and MNWS-C can be used in further research and clinical evaluation in Chinese smoking population with acceptable validity and reliability.

INVEST Fellow: Anton Bernalov, Russia, 1994 - 1995

Nikiforuk A, Popik P, Drescher KU, van Gaalen M, Relo AL, Mezler M, Marek G, Schoemaker H, Gross G, Bernalov A. Effects of a positive allosteric modulator of group II metabotropic glutamate receptors, LY487379, on cognitive flexibility and impulsive-like responding in rats.

Journal of Pharmacology and Experimental Therapeutics. 2010 Dec; 335(3): 665-673. Epub Aug 25.

Orthosteric group II metabotropic glutamate receptor (mGluR) agonists are regarded as novel, effective medications for all major symptom domains of schizophrenia, including cognitive disturbances. mGluR2s also can be affected in a more subtle way by positive allosteric modulators (PAMs) characterized by a unique degree of subtype selectivity and neuronal frequency-dependent activity. Because currently available treatments for schizophrenia do not improve cognitive dysfunction, the main aim of the present study was to examine the effects of a mGluR2 PAM, N-(4-(2-methoxyphenoxy)-phenyl)-N-(2,2,2-trifluoroethylsulfonyl)-pyrid-3-ylmethylamine (LY487379), on rat cognitive flexibility and impulsive-like responding, assessed in an attentional set-shifting task (ASST) and a differential reinforcement of low-rate 72 s (DRL72) schedule of food reinforcement. In addition, *in vivo* microdialysis was used to assess the drug's impact on cortical levels of dopamine, norepinephrine, serotonin, and glutamate. Rats treated with LY487379 (30 mg/kg) required significantly fewer trials to criteria during the extradimensional

shift phase of the ASST. Under a DRL72 schedule, LY487379 (30 mg/kg) decreased the response rate and increased the number of reinforcers obtained. These effects were accompanied by the shift of the frequency distribution of responses toward longer inter-response time durations. LY487379 significantly enhanced extracellular norepinephrine and serotonin levels in the medial prefrontal cortex. In summary, the present study demonstrates that a mGluR2 PAM, LY487379, promotes cognitive flexibility and facilitates behavioral inhibition. These procognitive effects may contribute to the therapeutic efficacy of agents stimulating mGluR2 in schizophrenia.

Banasikowski TJ, Bernalov A, Drescher K, Behl B, Unger L, Haupt A, Schoemaker H, Sullivan JP, Gross G, Beninger RJ. Double dissociation of the effects of haloperidol and the dopamine D3 receptor antagonist ABT-127 on acquisition vs. expression of cocaine-conditioned activity in rats. *Journal of Pharmacology and Experimental Therapeutics*. 2010 Nov; 335(2):506-515. Epub Aug 19. Dopamine receptors play a critical role in reward-related learning, but receptor subtypes may be differentially involved. D2-preferring receptor antagonists, e.g., haloperidol, attenuate acquisition of cocaine-conditioned motor activity at doses that fail to block expression. The authors compared haloperidol [4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one] with the D3 receptor-preferring antagonist 2,3-di-tert-butyl-6-{4-[3-(4,5-dimethyl-4H-[1,2,4] triazol-3-ylsulfanyl)-propyl]-piperazin-1-yl}-pyrimidine hydrochloride (ABT-127), given at D3 receptor-selective doses [i.e., no displacement of [(3)H]3,5-dichloro-N-[[2S]-1-ethyl-2-pyrrolidinyl] methyl]-2-hydroxy-6-methoxybenzamide binding, no effects on γ -butyrolactone-induced striatal l-3,4-dihydroxyphenylalanine; haloperidol accumulation; no attenuation of apomorphine-induced stereotypy]. They hypothesized that haloperidol and ABT-127 will produce a doubly dissociable effect on acquisition versus expression of cocaine-conditioned activity. Rats received three 1-h habituation sessions to activity monitors followed by three 1-h cocaine (10 mg/kg) conditioning sessions. The expression phase (no cocaine injections) took place 48 h later. Haloperidol (50 μ /kg) given during the conditioning phase blocked the acquisition of conditioned activity but failed to block the expression of conditioning when given on the test day. In contrast, ABT-127 (1.0 mg/kg), when given during conditioning, failed to block the acquisition of conditioned activity but blocked the expression of conditioning when administered on the test day. Results suggest that D2 receptors are more critically involved in acquisition than initial expression and D3 receptors are more critically involved in expression than acquisition of conditioned activity based on cocaine.

Hillen H, Barghorn S, Striebinger A, Labkovsky B, M \ddot{Y} ller R, Nimmrich V, Nolte MW, Perez-Cruz C, van der Auwera I, van Leuven F, van Gaalen M, Bernalov AY, Schoemaker H, Sullivan JP, Ebert U. Generation and therapeutic efficacy of highly oligomer-specific beta-amyloid antibodies. *Journal of Neuroscience*. 2010 Aug 4; 30(31): 10369-10379.

Oligomers of the beta-amyloid (A β) peptide have been indicated in early neuropathologic changes in Alzheimer's disease. Here, the authors present a synthetic A β (20-42) oligomer (named globulomer) with a different conformation to monomeric and fibrillar A β peptide, enabling the generation of highly A β oligomer-specific monoclonal antibodies. The globulomer-derived antibodies specifically detect oligomeric but not monomeric or fibrillar A β in various A β preparations. The globulomer-specific antibody A-887755 was able to prevent A β oligomer binding and dynamin cleavage in primary hippocampal neurons and to reverse globulomer-induced reduced synaptic transmission. In amyloid precursor protein (APP) transgenic mice, vaccination with A β globulomer and treatment with A-887755 improved novel object recognition. The cognitive improvement is likely attributable to reversing a deficit in hippocampal synaptic spine density in APP transgenic mice as observed after treatment with A-887755. Their findings demonstrate that selective reduction of A β oligomers by immunotherapy is sufficient to

normalize cognitive behavior and synaptic deficits in APP transgenic mice.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Research Findings - Intramural Research

Biomedical Informatics Section

PGIS: Electronic Diary Data Integration with GPS Data—Initial Application in Substance-Abuse Patients

Quantification of exposure to psychosocial stressors and drug availability might assist in the prevention and treatment of substance-use problems. The core of such interventions lies in combining real-time self-report data (via Ecological Momentary Assessment, EMA) with real-time geolocation data (via GPS logging). Combining these types of data and linking the result with patients' clinical research records has inherent technical challenges. In this paper, we describe how we have addressed those challenges via our Psychosocial Geolocation Integration System (PGIS), which we successfully used in two clinical studies involving polydrug-abusing participants. Vahabzadeh M, Mezghanni M, Lin JL, Epstein DH, Preston KL. Proc. 23rd IEEE International Symposium on Computer-Based Medical Systems (CBMS 2010), 2010; 489-494.

Behavioral Neuroscience

Expression of Heat Shock Protein (HSP 72 kDa) During Acute Methamphetamine Intoxication Depends on Brain Hyperthermia: Neurotoxicity or Neuroprotection?

In the present study, light and electron microscopy were used to examine heat shock protein (HSP 72kD) expression during acute methamphetamine (METH) intoxication in rats and evaluate its relationships with brain temperature and alterations in a number of other histochemical and morphological parameters. Freely moving rats received METH at the same dose (9 mg/kg, sc) but at different ambient temperatures (23 and 29°C), showing a wide range of brain temperature elevations (37.6-42.5°C); brains were taken for histochemical and morphological evaluations at peak of brain temperature increase. The authors found that acute METH intoxication induces massive and wide-spread HSP expression in neural and glial cells examined in detail in the cortex, hippocampus, thalamus, and hypothalamus. In each of these structures, the number of HSP-positive cells tightly correlated with brain temperature elevation. The changes in HSP immunoreactivity were also tightly related to alterations in permeability of the blood-brain barrier, acute glial activation, and brain edema assessed by albumin and GFAP immunoreactivity and measuring tissue water content, respectively. While robust and generalized HSP production normally appears to be the part of an adaptive brain response associated with METH-induced metabolic activation, activation of this protective mechanism has its natural limits and could not counteract the damaging effects of oxidative stress, high temperature, and edema—the leading factors of METH-induced neurotoxicity. Kiyatkin EA, Sharma HS. Journal of Neural Transmission.

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2010 Oct 8 (Epub ahead of print).

Extracellular Fluctuations of Dopamine and Glutamate in the Nucleus Accumbens Core and Shell Associated with Lever-Pressing During Cocaine Self-administration, Extinction, and Yoked Cocaine Administration

Dopamine and glutamate in the nucleus accumbens (NAS) are differentially implicated in cocaine-directed behavior. In this study, IRP scientists sought to compare extracellular fluctuations of dopamine and glutamate in core and shell of NAS associated with operant responding during cocaine self-administration, extinction, and yoked cocaine administration. Rats were trained to lever-press for cocaine or saline under FR1 before undergoing microdialysis testing during cocaine self-administration, extinction, or yoked cocaine administration.

Microdialysis samples were collected every 20 min and were analyzed for dopamine and glutamate with high-performance liquid chromatography. Rats actively lever-pressed during cocaine self-administration and extinction. However, lever-pressing was minimal during yoked cocaine administration in both cocaine-trained and saline-trained rats. Dopamine was elevated throughout cocaine self-administration and yoked cocaine administration. The extent of cocaine-evoked dopamine was greater in shell than in core, greater in cocaine-trained than in saline-trained rats, and greater during self-administration than during yoked administration. Dopamine was also elevated in core (first 60 min) and in shell (first 40 min) during extinction. Basal concentration of glutamate, but not dopamine, was lower in cocaine-trained than in saline-trained rats. In cocaine-trained rats, glutamate was elevated during cocaine self-administration and extinction but was depressed below baseline during yoked cocaine administration. The extent and direction of glutamate fluctuation was similar between core and shell. In saline-trained rats, glutamate was not affected by yoked cocaine. The authors conclude that distinct patterns of dopamine and glutamate fluctuations in core and shell appear to underlie characteristic patterns of lever-pressing associated with cocaine self-administration, extinction, and yoked cocaine administration. Suto N, Ecke LE, You Z-B, Wise RA. *Psychopharmacology*. 2010 Aug; 211(3):267-275.

Rapid EEG Desynchronization and EMG Activation Induced by Intravenous Cocaine in Freely Moving Rats: A Peripheral, Non-Dopamine Neural Triggering?

Many important physiological, behavioral and psychoemotional effects of intravenous (iv) cocaine (COC) are too fast and transient when compared to pharmacokinetic predictions, suggesting a possible involvement of peripheral neural mechanisms in their triggering. In the present study, IRP researchers examined changes in cortical electroencephalogram (EEG) and neck electromyogram (EMG) induced in freely moving rats by iv COC administration at low, reinforcing doses (0.25-1.0 mg/kg) and compared them with those induced by an auditory stimulus and iv COC methiodide which cannot cross the blood-brain barrier. The authors found that COC induces rapid, strong, and prolonged EEG desynchronization, associated with decrease in alpha and increase in beta and gamma activities, and EMG activation that both begin within 2-6 s following the start of a 10-s injection; immediate components of this effect were dose-independent. The rapid COC-induced changes in EEG and EMG resembled those induced by an auditory stimulus; the latter effects had shorter onset latencies and durations and were fully blocked during urethane anesthesia. Although urethane anesthesia completely blocked COC-induced EMG activation and rapid components of EEG response, COC still induced EEG desynchronization that was much weaker, greatly delayed (~60 s), and associated with tonic decreases in delta and increases in alpha, beta and gamma activities. Surprisingly, iv saline delivered during slow-wave sleep (but not quite wakefulness) also induced a transient EEG desynchronization but without changes in EMG activity; these effects were also fully blocked during anesthesia. Peripherally acting COC methiodide fully mimicked rapid EEG and

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EMG effects of regular COC, but the effects at an equimolar dose were less prolonged than those with regular COC. These data suggest that in awake animals iv COC, like somato-sensory stimuli, induces cortical activation and a subsequent motor response via its action on peripheral neural elements and involving rapid neural transmission. By providing a rapid neural signal and triggering transient neural activation, such an action might play a crucial role in the sensory effects of COC, thus contributing to the learning and development of drug-taking behavior. Kiyatkin, EA, Smirnov MS. American Journal of Physiology. 2010; 298: R285-R300.

Neurobiology of Relapse Section

Incubation of Conditioned Fear in the Conditioned Suppression Model in Rats: Role of Food-Restriction Conditions, Length of Conditioned Stimulus, and Generality to Conditioned Freezing

IRP investigators recently adapted the conditioned suppression of operant responding method to study fear incubation. They found that food-restricted rats show low fear 2 days after extended (10 d; 100 30-s tone-shock pairings) fear training and high fear after 1-2 months. Here, they studied a potential mechanism of fear incubation: extended food-restriction stress. They also studied whether fear incubation is observed after fear training with a prolonged-duration (6-min) tone conditioned stimulus (CS), and whether conditioned freezing incubates after extended training in rats with or without a concurrent operant task. Conditioned fear was assessed 2 days and 1 month after training. In the conditioned suppression method, fear incubation was reliably observed in rats under moderate food-restriction conditions (18-20 g food/day) that allowed for weight gain, and after extended (10 d), but not limited (1 d), fear training with the 6-min CS. Incubation of conditioned freezing was observed after extended fear training in rats lever-pressing for food and, to a lesser degree, in rats not performing an operant task. Results indicate that prolonged hunger-related stress does not account for fear incubation in the conditioned suppression method, and that fear incubation occurs to a longer-duration (6-min) fear CS. Extended training also leads to robust fear incubation of conditioned freezing in rats performing an operant task and weaker fear incubation in rats not performing an operant task. Pickens CL, Navarre BM, Nair SG. Neuroscience. 2010 Sep 15; 169(4): 1501-1510.

Clinical Pharmacology and Therapeutics

Incubation of Cue-Induced Cigarette Craving During Abstinence in Human Smokers

Abstinent drug users remain at risk for relapse long after withdrawal subsides. Animal studies indicate that responses to drug-related cues not only persist but increase with abstinence, a phenomenon termed "incubation of drug craving." It is unknown whether cue-induced craving increases, decreases, or remains constant with abstinence in humans. Here, IRP scientists investigated effects of abstinence on cue-induced craving in cigarette smokers. Eighty-six non-treatment-seeking, adult smokers (≥ 10 cigarettes daily) were paid to abstain for 7 (Group 1), 14 (Group 2), or 35 (Groups 3 and 4) days. Abstinence was verified daily. Groups 1, 2, and 3 underwent a single cue session on the final abstinence day (7, 14, or 35). Group 4 viewed cues on Days 7, 14, and 35. Between and within groups, smoking-cue-induced craving increased with abstinence on some measures. Cue-induced craving was greater in Group 3 (35-day) compared with Group 1 (7-day). Within Group 4, cue-induced craving was greater at 35 than 14 days. Cue-induced craving did not decrease with abstinence on any measure. The authors present initial evidence of incubation of cue-induced craving in humans. The observation that cue-induced craving increases with abstinence, even as "background" craving and withdrawal symptoms subside, might have treatment implications. Bedi G, Preston KL,

Epstein DH, Heishman SJ, Marrone GF, Shaham Y, de Wit H. *Biol Psychiatry*. 2010 Sep 2. [Epub ahead of print].

Nicotine Psychopharmacology Section/Clinical Pharmacology and Therapeutics Branch

Quantitative Analysis of Tobacco Withdrawal

Previous studies have documented the existence of signs and symptoms of the acute tobacco abstinence syndrome; however, less attention has been paid to quantifying the magnitude of these effects. The present study quantified the relative magnitude of subjective, cognitive, and physiological manifestations of acute tobacco abstinence. Smokers (N=203, ³15 cig/day) attended two counterbalanced laboratory sessions, one following 12-h of abstinence and the other following ad-lib smoking. At both sessions, they completed an extensive battery of self-report measures (withdrawal, affect, hunger, craving, subjective attentional bias towards smoking cues), physiological assessments (heart rate, blood pressure, brain EEG), and cognitive performance tasks (psychomotor processing, sustained attention, objective attentional bias). Abstinence effects were largest for craving, subjective attentional bias, negative affect, overall withdrawal severity, concentration difficulty, hunger, and heart rate. Effects were moderate for positive affect and EEG power. Effects were small, but reliable, for psychomotor speed, sustained attention, and somatic symptoms. Effects on performance-based indices of attentional bias towards smoking-related cues were small and reliable for some indices, but not others. Effects were small and inconsistent for blood pressure and EEG frequency. Variation in internal consistency accounted for 33% of the variation in abstinence effect sizes across measures. There was a wide range of effect sizes both across and within domains, indicating that the acute tobacco abstinence syndrome is not a monotonic phenomenon. These findings may be indicative of the relative magnitudes of signs and symptoms that the average smoker may exhibit during acute abstinence. Leventhal AM, Waters AJ, Moolchan ET, Heishman SJ, Pickworth WB. A quantitative analysis of subjective, cognitive, and physiological manifestations of the acute tobacco abstinence syndrome. *Addict Behav* 2010; 35: 1120-1130.

Chemical Biology Research Branch, Drug Design and Synthesis Section

Selective Enhancement of Fentanyl-induced Antinociception by the Delta Agonist SNC162 but not by Ketamine in Rhesus Monkeys: Further Evidence Supportive of Delta Agonists as Candidate Adjuncts to Mu Opioid Analgesics

Mu-opioid receptor agonists such as fentanyl are effective analgesics, but their clinical use is limited by untoward effects. Adjunct medications may improve the effectiveness and/or safety of opioid analgesics. This study compared interactions between fentanyl and either the noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine or the delta-opioid receptor agonist SNC162 [(+)-4-[(alphaR)-alpha-[(2S,5R)-2,5-dimethyl-4-(2-propenyl)-1-piperazinyl]-(3-phenyl)methyl]-N,N-diethylbenzamide] in two behavioral assays in rhesus monkeys. An assay of thermal nociception evaluated tail-withdrawal latencies from water heated to 50 and 54°C. An assay of schedule-controlled responding evaluated response rates maintained under a fixed-ratio 30 schedule of food presentation. Effects of each drug alone and of three mixtures of ketamine+fentanyl (22:1, 65:1, 195:1 ketamine/fentanyl) or SNC162+fentanyl (59:1, 176:1, 528:1 SNC162/fentanyl) were evaluated in each assay. All drugs and mixtures dose-dependently decreased rates of food-maintained responding, and drug proportions in the mixtures were based on relative potencies in this assay. Ketamine and SNC162 were inactive in the assay of thermal antinociception, but fentanyl and all mixtures produced dose-dependent antinociception. Drug interactions were evaluated using dose-

addition and dose-ratio analysis. Dose-addition analysis revealed that interactions for all ketamine/fentanyl mixtures were additive in both assays. SNC162/fentanyl interactions were usually additive, but one mixture (176:1) produced synergistic antinociception at 50°C. Dose-ratio analysis indicated that ketamine failed to improve the relative potency of fentanyl to produce antinociception vs. rate suppression, whereas two SNC162/fentanyl mixtures (59:1 and 176:1) increased the relative potency of fentanyl to produce antinociception. These results suggest that delta agonists may produce more selective enhancement than ketamine of mu agonist-induced antinociception. Banks ML, Folk JE, Rice KC, Negus SS. *Pharmacol Biochem Behav.* 2010 Dec; 97(2): 205-212. Epub 2010 Aug 3.

Interaction of 5-HT_{2A} and 5-HT_{2C} Receptors in R(-)-2,5-dimethoxy-4-iodoamphetamine-elicited Head Twitch Behavior in Mice

Drug-elicited head-twitch behavior is a useful model for studying hallucinogen activity at 5-HT_{2A} receptors in the mouse. Chemically diverse compounds active in this assay yield biphasic dose-effect curves, but there is no compelling explanation for the "descending" portion of these functions. A set of experiments was designed to test the hypothesis that the induction of head-twitch behavior is mediated by agonist actions at 5-HT_{2A} receptors, whereas the inhibition of head-twitch behavior observed at higher doses results from competing agonist activity at 5-HT_{2C} receptors. The effects of the phenethylamine hallucinogen R(-)-2,5-dimethoxy-4-iodoamphetamine (DOI) on head-twitch behavior were studied over a range of doses in the mouse, generating a characteristic biphasic dose-response curve. Pretreatment with the selective 5-HT_{2A} antagonist (+)-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol (M100907) shifted only the ascending limb of the DOI dose-effect function, whereas pretreatment with the nonselective 5-HT_{2A/2C} antagonist 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}quinazoline-2,4(1H,3H)-dione (ketanserin) produced a parallel shift to the right in the DOI dose-response curve. Administration of the 5-HT_{2C} agonist S-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine (Ro 60-0175) noncompetitively inhibited DOI-elicited head-twitch behavior across the entire dose-effect function. Finally, pretreatment with the selective 5-HT_{2C} antagonists 6-chloro-5-methyl-1-[(2-[2-methylpyrid-3-yloxy]pyrid-5yl)carbonyl]indoline (SB242084) or 8-[5-(2,4-dimethoxy-5-(4-trifluoromethylphenylsulfonamido)phenyl-5-oxopentyl)-1,3,8-triazaspiro[4,5]decane-2,4-dione hydrochloride (RS 102221) did not alter DOI-elicited head-twitch behavior on the ascending limb of the dose-response curve but shifted the descending limb of the DOI dose-response function to the right. The results of these experiments provide strong evidence that DOI-elicited head-twitch behavior is a 5-HT_{2A} agonist-mediated effect, with subsequent inhibition of head-twitch behavior being driven by competing 5-HT_{2C} agonist activity. Fantegrossi WE, Simoneau J, Cohen MS, Zimmerman SM, Henson CM, Rice KC, Woods JH. *J Pharmacol Exp Ther.* 2010 Dec; 335(3): 728-734. Epub 2010 Sep 21.

Medications Discovery Research Branch, Medicinal Chemistry Section

Structural Basis of Pharmacological Specificity Between Dopamine D₂ and D₃ Receptors is Revealed by the D₃ Receptor Crystal Structure

Dopamine modulates movement, cognitive, and emotional functions through activation of dopamine G protein-coupled receptors (GPCR) in the brain. The crystal structure of the human dopamine D₃ receptor (D₃R) in complex with the small molecule D₂R/D₃R-specific antagonist eticlopride at 3.2 Å resolution reveals important features of the ligand binding pocket and extracellular loops. On the intracellular side of the receptor, a locked conformation of the ionic lock and two distinctly different conformations of intracellular loop 2 are observed. Docking of R-22, a D₃R-selective antagonist to the D₃R structure reveals an

extracellular extension of the eticlopride binding site that comprises a connected second binding pocket for the aryl amide of R-22, which differs between the highly homologous D2R and D3R. This difference provides direction to the design of D3R-selective agents for treating drug abuse and other neuropsychiatric disorders. Chien YET, Liu W, Zhao Q, Katritch V, Hanson MA, Shi L, Newman AH, Javitch JA, Cherezov V, Stevens RC. Structure of the Human Dopamine D3 Receptor in Complex with a D2/D3 Selective Antagonist. *Science*. 2010; 333(6047): 1091-1095.

Novel Citalopram Analogues as Probes for the Serotonin Transporter

(±)-Citalopram and its eutomer, escitalopram (S(+)-1) are selective serotonin reuptake inhibitors (SSRIs) that are used clinically to treat anxiety and depression. To further explore structure-activity relationships at the serotonin transporter (SERT), a series of (±)-4- and 5-substituted citalopram analogues were designed, synthesized and evaluated for binding at the SERT, dopamine transporter (DAT) and norepinephrine transporter (NET) in native rodent tissue. Many of these analogues showed high SERT binding affinities ($K_i = 1-40$ nM) and selectivities over both NET and DAT. Selected enantiomeric pairs of analogues were synthesized and both retained enantioselectivity as with S- and R-citalopram, wherein $S > R$ at the SERT. In addition, the enantiomeric pairs of citalopram and analogues were tested for binding at the homologous bacterial Leucine transporter (LeuT), wherein low affinities and the absence of enantioselectivity suggested distinctive binding sites for these compounds at SERT as compared to LeuT. These novel ligands will provide molecular tools to elucidate drug-protein interactions at the SERT and to relate those to behavioral actions, *in vivo*. Zhang P, Cyriac G, Kopajtic T, Zhao Y, Javitch JA, Katz JL, Newman AH. Structure-Activity Relationships for a Novel Series of Citalopram (1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile) Analogues at Monoamine Transporters. *J Med Chem*. 2010; 53(16): 6112-6121.

The D3 Dopamine Receptor Selective Agonist/Partial Agonist PG01042 Attenuates L-Dopa Dependent Animal Involuntary Movements in Rats

The substituted 4-phenylpiperazine D3 dopamine receptor selective antagonist was recently reported to attenuate L-DOPA associated abnormal involuntary movements (AIMs) in unilaterally lesioned rats, a model of L-DOPA-dependent dyskinesia in patients with Parkinson's Disease. IRP scientists now report that PG01042, which is a D3 dopamine receptor selective agonist for adenylyl cyclase inhibition and a partial agonist for mitogenesis, is also capable of attenuating AIM scores. The intrinsic activity of PG01037 and PG01042 were determined using a) a forskolin-dependent adenylyl cyclase inhibition assay and b) an assay for agonist-associated mitogenesis. It was observed that the *in vivo* efficacy of PG01042 increased when administered by intraperitoneal (i.p.) injection simultaneously with L-DOPA/benserazide (8 mg/kg each), as compared to a 60 minute pretreatment. PG01042 was found to attenuate AIM scores in these animals in a dose dependent manner. Rotarod studies indicate that PG01042 at a dose of 10 mg/kg did not adversely affect motor coordination of the unilaterally lesioned rats. Evaluation of lesioned rats using a cylinder test behavioral paradigm indicated that PG01042 did not dramatically attenuate the beneficial effects of L-DOPA. These studies and previously published studies suggest that both D3 dopamine receptor selective antagonists, partial agonists and agonists, as defined by an adenylyl cyclase inhibition assay and a mitogenic assay, are pharmacotherapeutic candidates for the treatment of L-DOPA-associated dyskinesia in patients with Parkinson's Disease. Riddle LR, Kumar R, Griffin SA, Grundt P, Newman AH, Luedtke RR. Evaluation of the D3 dopamine receptor selective agonist/partial agonist PG01042 on L-Dopa dependent animal involuntary movements in rats. *Neuropharmacology*. 2010; e-pub Sept. 17, 2010.

Novel Modafinil Analogues as Atypical Dopamine Uptake Inhibitors

Modafinil is used clinically as a wake-promoting agent for the treatment of

narcolepsy and other sleep disorders. It has recently been studied as a potential medication to treat psychostimulant abuse with mixed results. To further understand how modafinil effects its behavioral actions and potentially improve its utility as a therapeutic, a series of analogues was synthesized to investigate the effects of chemical modifications on dopamine, serotonin and norepinephrine transporter binding. In addition, the locomotor-stimulant effects in mice of (\pm)-modafinil, its R- and S-enantiomers and a novel analogue were compared to those of cocaine. Structure-activity relationships suggest binding interactions at the DAT that appear to contrast to the benztropine analogues, which also have a biphenyl structural motif and behave as atypical dopamine uptake inhibitors, *in vivo*. Studies of locomotor activity in mice suggests behavioral stimulant effects, though the effectiveness of the drugs studied was less than that of cocaine, but greater than that of many benztropine analogues. The results of the present studies warrant further investigation of these and other modafinil analogues in additional animal models of psychostimulant abuse. Cao J, Prisinzano TE, Okunola OM, Kopajtic T, Shook M, Katz JL, Newman AH. Structure-Activity Relationships at the Monoamine Transporters for a Novel Series of Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) Analogues. *A. C. S. Med. Chem. Lett.* 2010, e-pub October 18, 2010.

Molecular Neurobiology Branch

Personalized Smoking Cessation: Interactions Between Nicotine Dose, Dependence and Quit-Success Genotype Score

Genetic determinants account for half of individual differences in ability to quit smoking. This paper provides results from a clinical trial of smoking cessation that substantially validate prior work using pooling approaches and add to our confidence in a group of SNP markers that can help to predict smoking cessation success. Rose JE, Behm FM, Drgon T, Johnson C, Uhl GR. *Mol Med.* 2010 Jul-Aug; 16(7-8): 247-253. Epub 2010 Mar 17. PMID: 2037961

Genome-Wide Association for Smoking Cessation Success: Participants in the Patch in Practice Trial of Nicotine Replacement

This work describes genome wide association data for ability to quit smoking in general practice settings. These data confirm many results from prior MNB smoking cessation genome wide association studies. In this work, there is no evidence for genes of major effect, but rather evidence for polygenic effects with substantial allelic heterogeneity, as is likely to be the case for most genetic influences on brain disorders. Uhl GR, Drgon T, Johnson C, Walther D, David SP, Aveyard P, Murphy M, Johnstone EC, Munaf[~] MR. *Pharmacogenomics.* 2010 Mar; 11(3): 357-367 PMID: 20235792

A Greater Role for the Norepinephrine Transporter than the Serotonin Transporter in Nociception

Descending brain systems using NE (norepinephrine) and 5HT (serotonin) have long been implication in modulating pain, but the relative contributions of these two systems have remained controversial. This paper reports knockout mouse studies that support roles for both, but a larger role for NE systems, in these mice, than would have been previously anticipated. Since NE and 5HT drugs remain among the most widely used nonopiate approaches to managing moderate chronic pain, these findings have substantial therapeutic implications for humans. Hall FS, Schwarzbaum JM, Perona MT, Templin JS, Caron MG, Lesch KP, Murphy DL, Uhl GR. *Neuroscience.* 2010 Dec 1. [Epub ahead of print] PMID: 21129446

Antidepressant-like Effect of Venlafaxine is Abolished in μ -opioid Receptor-Knockout Mice

Agents that target norepinephrine/serotonin brain systems, including venlafaxine, provide antidepressant responses in several tests that can predict efficacy for drugs that are clinically useful in depression. This collaborative study provides some of the first evidence that deletion of mu opiate receptors

alters these responses. Ide S, Fujiwara S, Fujiwara M, Sora I, Ikeda K, Minami M, Uhl GR, Ishihara K. *J Pharmacol Sci.* 2010 Sep 16;114(1):107-10. Epub 2010 Aug 10. PMID: 20703010

Dopamine D4 Receptor Gene Variation Moderates the Efficacy of Bupropion for Smoking Cessation

The smoking cessation aid bupropion acts on dopamine and, with lower potency nicotinic brain systems. In this collaborative study, a DRD4 dopamine system gene variant that substantially alters the function of this brain dopamine receptor is associated with ability to quit in bupropion-treated smokers who seek treatment in a randomized controlled clinical trial. Leventhal AM, David SP, Brightman M, Strong D, McGeary JE, Brown RA, Lloyd-Richardson EE, Munaf^ˆ M, Uhl GR, Niaura R. *Pharmacogenomics J.* 2010 Jul 27. [PMID: 20661272]

Altered Neurocircuitry in the Dopamine Transporter Knockout Mouse Brain

There are a constellation of behavioral changes that IRP scientists and others have identified in mice that we have produced that display deletions of the gene for the dopamine transporter. This collaborative study provides the most detailed imaging study of the brains of these animals, ruling out gross changes in brain structure and white matter organization, but identifying more subtle changes in imaging patterns that can be identified with methods newly developed for imaging these small brains. Zhang X, Bearer EL, Boulat B, Hall FS, Uhl GR, Jacobs RE. *PLoS One.* 2010 Jul 9;5(7):e11506. PMID: 20634895

Fine Mapping of Calcineurin (PPP3CA) Gene Reveals Novel Alternative Splicing Patterns, Association of 5'UTR Trinucleotide Repeat with Addiction Vulnerability, and Differential Isoform Expression in Alzheimer's Disease

Calcineurin is a plausible addiction vulnerability candidate gene. These results provide very modest evidence for calcineurin association with addiction vulnerability. Chiocco MJ, Zhu X, Walther D, Pletnikova O, Troncoso JC, Uhl GR, Liu QR. *Subst Use Misuse.* 2010 Sep;45(11): 1809-1826. PMID: 20590401

Dietary Restriction Mitigates Cocaine-induced Alterations of Olfactory Bulb Cellular Plasticity and Gene Expression, and Behavior

Dietary restriction provides a plausible interactive effects on brain plasticity and drug effects. In this collaborative work, mice with dietary restriction display modest effects on cocaine reward, with larger influences on olfactory bulb neurogenesis. Xu X, Mughal MR, Scott Hall F, Perona MT, Pistell PJ, Lathia JD, Chigurupati S, Becker KG, Ladenheim B, Niklason LE, Uhl GR, Cadet JL, Mattson MP. *J Neurochem.* 2010 Jul;114(1): 323-334. Epub 2010 Apr 29. PMID: 20456017

A Human-Specific De Novo Protein-Coding Gene Associated with Human Brain Functions

This collaborative work describes a gene identified only in humans that is expressed in brain. Li CY, Zhang Y, Wang Z, Zhang Y, Cao C, Zhang PW, Lu SJ, Li XM, Yu Q, Zheng X, Du Q, Uhl GR, Liu QR, Wei L. *PLoS Comput Biol.* 2010 Mar 26;6(3):e1000734. PMID: 20376170

Integrative Neuroscience Research Branch

Shift from Goal-directed to Habitual Cocaine Seeking after Prolonged Experience in Rats

The development of drug seeking habits is implicated in the transition from recreational drug use to addiction. To this date, however, few studies have addressed the role of habit learning in drug seeking. The canonical test used to evaluate habitual behavior is the devaluation procedure which relies on the poor sensitivity of habitual behavior to its consequences. In this test,

devaluation of the outcome results in decreased responding when the behavior evaluated is a goal-directed action, but little change in responding is observed when the behavior has become habitual. IRP scientists adapted a drug seeking/taking chained schedule of intravenous cocaine self-administration together with an outcome devaluation procedure to study habitual drug seeking in rats. In this paradigm, responding on a designated drug seeking lever affords access to a drug taking lever, which results in a drug infusion. The present studies examined whether drug-seeking that is initially goal-directed becomes habitual after prolonged drug seeking and taking. Devaluation of the outcome of the drug seeking link (i.e. the drug taking link of the chained schedule) by extinction significantly decreased drug seeking indicating that behavior is goal-directed rather than habitual. With, however, more prolonged drug experience, animals transitioned to habitual cocaine seeking. Thus, in these animals, cocaine-seeking was insensitive to outcome devaluation. Moreover, when the dorsolateral striatum, an area implicated in habit learning, was transiently inactivated, outcome devaluation was effective in decreasing drug-seeking indicating that responding was no longer habitual but had reverted to control by the goal-directed system. These studies provide direct evidence that cocaine seeking becomes habitual with prolonged drug experience and describe a rodent model with which to study the neural mechanisms underlying the transition from goal-directed to habitual drug-seeking. Furthermore, the observation that habitual cocaine seeking reverts to a goal-directed action after dorsal striatum inactivation suggests that drug seeking habits are reversible. Zapata A, Minney VL and Shippenberg TS. Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats. *J Neurosci.* 2010; 30(46): 15457-15463.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Regulation of σ -1 Receptors and Endoplasmic Reticulum Chaperones in the Brain of Methamphetamine Self-administering Rats

Sigma-1 receptors are endoplasmic reticulum (ER) chaperones that are implicated in the neuroplasticity associated with psychostimulant abuse. IRP investigators immunocytochemically examined the distribution of sigma-1 receptors in the brain of drug-naive rats and then examined the dynamics of sigma-1 receptors and other ER chaperones in specific brain subregions of rats that self-administered methamphetamine, received methamphetamine passively, or received only saline injections. sigma-1 Receptors were found to be expressed in moderate to high levels in the olfactory bulb, striatum, nucleus accumbens shell, olfactory tubercle, amygdala, hippocampus, red nucleus, ventral tegmental area, substantia nigra, and locus ceruleus.

Methamphetamine, whether self-administered or passively received, significantly elevated ER chaperones including the sigma-1 receptor, BiP, and calreticulin in the ventral tegmental area and substantia nigra. In the olfactory bulb, however, only the sigma-1 receptor chaperone was increased, and this increase occurred only in rats that actively self-administered methamphetamine. Consistent with an increase in sigma-1 receptors, extracellular signal-regulated kinase was found to be activated and protein kinase A attenuated in the olfactory bulb of methamphetamine self-administering rats. sigma-1 Receptors in the olfactory bulb were found to be colocalized with dopamine D1 receptors. These results indicate that methamphetamine induces ER stress in the ventral tegmental area and substantia nigra in rats whether the drug is received actively or passively. However, the changes seen only in rats that actively self-administered methamphetamine suggest that D1 and sigma-1 receptors in the olfactory bulb might play an important role in the motivational conditioning/learning aspects of methamphetamine self-administration in the rat. Hayashi T, Justinova Z, Hayashi E, Cormaci G, Mori T, Tsai SY, Barnes C, Goldberg SR, Su SP. Regulation of σ -1 Receptors and Endoplasmic Reticulum Chaperones in the

Brain of Methamphetamine Self-Administering Rats. *Journal of Pharmacology and Experimental Therapeutics*, 2010; 332(3):1054-1063.

Noradrenergic α 1 Receptors as a Novel Target for the Treatment of Nicotine Addiction

Nicotine is the main psychoactive ingredient in tobacco and its rewarding effects are considered primarily responsible for persistent tobacco smoking and relapse. Although dopamine has been extensively implicated in the rewarding effects of nicotine, noradrenergic systems may have a larger role than previously suspected. This study evaluated the role of noradrenergic alpha(1) receptors in nicotine and food self-administration and relapse, nicotine discrimination, and nicotine-induced dopamine release in the nucleus accumbens in rats. The authors found that the noradrenergic alpha(1) receptor antagonist prazosin (0.25-1 mg/kg) dose dependently reduced the self-administration of nicotine (0.03 mg/kg), an effect that was maintained over consecutive daily sessions; but did not reduce food self-administration. Prazosin also decreased reinstatement of extinguished nicotine seeking induced by either a nicotine prime (0.15 mg/kg) or nicotine-associated cues, but not food-induced reinstatement of food-seeking, and decreased nicotine-induced (0.15 mg/kg) dopamine release in the nucleus accumbens shell. However, prazosin did not have nicotine-like discriminative effects and did not alter the dose-response curve for nicotine discrimination. These findings suggest that stimulation of noradrenergic alpha(1) receptors is involved in nicotine self-administration and relapse, possibly via facilitation of nicotine-induced activation of the mesolimbic dopaminergic system. The findings point to alpha(1) adrenoceptor blockade as a potential new approach to the treatment of tobacco dependence in humans. Forget B, Wertheim C, Mascia P, Goldberg SR, Le Foll B. Noradrenergic α 1 receptors as a novel target for the treatment of nicotine addiction. *Neuropsychopharmacology*, 2010; 35(8): 1751-1760.

Adenosine-Cannabinoid Receptor Interactions: Implications for Striatal Function

Adenosine and endocannabinoids are very ubiquitous non-classical neurotransmitters that exert a modulatory role on the transmission of other more 'classical' neurotransmitters. In this review IRP scientists focused on their common role as modulators of dopamine and glutamate neurotransmission in the striatum, the main input structure of the basal ganglia. They paid particular attention to the role of adenosine A(2A) receptors and cannabinoid CB(1) receptors. Experimental results suggest that presynaptic CB(1) receptors interacting with A(2A) receptors in cortico-striatal glutamatergic terminals that make synaptic contact with dynorphinergic medium-sized spiny neurons (MSNs) are involved in the motor-depressant and addictive effects of cannabinoids. On the other hand, postsynaptic CB(1) receptors interacting with A(2A) and D(2) receptors in the dendritic spines of enkephalinergic MSNs and postsynaptic CB(1) receptors in the dendritic spines of dynorphinergic MSN are probably involved in the cataleptogenic effects of cannabinoids. These receptor interactions most probably depend on the existence of a variety of heteromers of A(2A), CB(1) and D(2) receptors in different elements of striatal spine modules. Drugs selective for the different striatal A(2A) and CB(1) receptor heteromers could be used for the treatment of neuropsychiatric disorders and drug addiction and they could provide effective drugs with fewer side effects than currently used drugs. Ferré S, Lluís C, Justinova Z, Quiroz C, Orru M, Navarro G, Franco R, Goldberg SR. Adenosine-cannabinoid receptor interactions. Implications for striatal function. *British Journal of Pharmacology*, 2010; 160: 443-453.

Peroxisome Proliferator-Activated Receptors-alpha (PPAR α) Modulate Dopamine Neuron Activity through Nicotinic Receptors

Modulation of midbrain dopamine neurons by nicotinic acetylcholine receptors (nAChRs) plays an important role in behavior, cognition, motivation, and reward. Specifically, nAChRs containing beta2 subunits (beta2-nAChRs) switch

dopamine cells from a resting to an excited state. However, how beta2-nAChRs can be modulated and thereby how dopamine firing activity is affected remains elusive. Because changes in dopamine cell activity are reflected in the dynamics of microcircuits generating altered responses to stimuli and inputs, factors regulating their state are fundamental. Among these, endogenous ligands to the nuclear receptor-transcription factor peroxisome proliferator-activated receptors type-alpha (PPARalpha) have been recently found to suppress nicotine-induced responses of dopamine neurons. IRP scientists used both in vitro and in vivo electrophysiological techniques together with behavioral analysis to investigate on the effects of modulation of PPARalpha in Sprague-Dawley rat and C57BLJ/6 mouse dopamine neurons and their interactions with beta2-nAChRs. To this aim, the authors took advantage of a selective reexpression of beta2-nAChR exclusively in dopamine cells by stereotaxically injecting a lentiviral vector in the mouse ventral tegmental area. They found that activation of PPARalpha decreases in vitro both dopamine cell activity and ventral tegmental area net output through negative modulation of beta2-nAChRs. Additionally, PPARalpha activation in vivo reduces both the number of spontaneously active dopamine neurons and nicotine-induced increased locomotion. The authors' combined findings suggest PPARalpha ligands as important negative modulators of beta2-nAChRs on dopamine neurons. Thus, PPARalpha ligands might prove beneficial in treating disorders in which dopamine dysfunction plays a prominent role, such as schizophrenia and nicotine addiction. Melis M, Carta S, Fattore L, Tolu S, Yasar S, Goldberg SR, Fratta W, Maskos U, Pistis M. Peroxisome proliferator-activated receptors-alpha (PPARalpha) modulate dopamine neuron activity through nicotinic receptors. *Biological Psychiatry*. 2010; 68(3): 256-264.

Animal Models of Cannabinoid Reward

The endogenous cannabinoid system is involved in numerous physiological and neuropsychological functions. Medications that target this system hold promise for the treatment of a wide variety of disorders. However, as reward is one of the most prominent of these functions, medications that activate this system must be evaluated for abuse potential. Meanwhile, cannabis is already being used chronically by millions of people, many of whom eventually seek treatment for cannabis dependence. Therefore, there is a need for procedures that can be used to: (i) better understand the mechanisms of cannabinoid reward; (ii) evaluate the abuse potential of new medications; and (iii) evaluate the effectiveness of medications developed for treating cannabis dependence. Animal models of cannabinoid reward provide a means of accomplishing these goals. In this review, the authors briefly describe and evaluate these models, their advantages and their shortcomings. Special emphasis is placed on intravenous cannabinoid self-administration in squirrel monkeys, a valid, reliable and flexible model that we have developed over the past decade. Although the conditions under which cannabinoid drugs have rewarding effects may be more restricted than with other drugs of abuse such as cocaine and heroin, work with these models indicates that cannabinoid reward involves similar brain mechanisms and produces the same kinds of reward-related behaviour. By continuing to use these animal models as tools in the development of new medications, it should be possible to take advantage of the potential benefits provided by the endocannabinoid system while minimizing its potential for harm. Panlilio LV, Justinova Z, Goldberg SR. Animal models of cannabinoid reward. *British Journal of Pharmacology*, 2010; 160: 499-510.

Effects of Fatty Acid Amide Hydrolase Inhibition on Neuronal Responses to Nicotine, Cocaine and Morphine in the Nucleus Accumbens Shell and Ventral Tegmental Area: Involvement of PPAR- α Nuclear Receptors

The endocannabinoid system regulates neurotransmission in brain regions relevant to neurobiological and behavioral actions of addicting drugs. IRP scientists recently demonstrated that inhibition by URB597 of fatty acid amide

hydrolase (FAAH), the main enzyme that degrades the endogenous cannabinoid N-acyl ethanolamine (NAE) anandamide and the endogenous non-cannabinoid NAEs oleoylethanolamide and palmitoylethanolamide, blocks nicotine-induced excitation of ventral tegmental area (VTA) dopamine (DA) neurons and DA release in the shell of the nucleus accumbens (ShNAc), as well as nicotine-induced drug self-administration, conditioned place preference and relapse in rats. Here, the authors studied whether effects of FAAH inhibition on nicotine-induced changes in activity of VTA DA neurons were specific for nicotine or extended to two drugs of abuse acting through different mechanisms, cocaine and morphine. They also evaluated whether FAAH inhibition affects nicotine-, cocaine- or morphine-induced actions in the ShNAc. Experiments involved single-unit electrophysiological recordings from DA neurons in the VTA and medium spiny neurons in the ShNAc in anesthetized rats. They found that URB597 blocked effects of nicotine and cocaine in the ShNAc through activation of both surface cannabinoid CB1-receptors and alpha-type peroxisome proliferator-activated nuclear receptor. URB597 did not alter the effects of either cocaine or morphine on VTA DA neurons. These results show that the blockade of nicotine-induced excitation of VTA DA neurons, which we previously described, is selective for nicotine and indicate novel mechanisms recruited to regulate the effects of addicting drugs within the ShNAc of the brain reward system. Luchicchi A, Lecca S, Carta S, Pillolla G, Muntoni AL, Yasar S, Goldberg SR, Pistis M. Effects of fatty acid amide hydrolase inhibition on neuronal responses to nicotine, cocaine and morphine in the nucleus accumbens shell and ventral tegmental area: involvement of PPAR- α nuclear receptors. *Addiction Biology*. 2010; 15(3): 277-288.

Blockade of Nicotine Reward and Relapse by Activation of Alpha-Type Peroxisome Proliferator-activated Receptors (PPAR- α)

Recent findings indicate that inhibitors of fatty acid amide hydrolase (FAAH) counteract the rewarding effects of nicotine in rats. Inhibition of FAAH increases levels of several endogenous substances in the brain, including the endocannabinoid anandamide and the noncannabinoid fatty acid ethanolamides oleoylethanolamide (OEA) and palmitoylethanolamide, which are ligands for alpha-type peroxisome proliferator-activated nuclear receptors (PPAR-alpha). Here, IRP researchers evaluated whether directly acting PPAR-alpha agonists can modulate reward-related effects of nicotine. The authors combined behavioral, neurochemical, and electrophysiological approaches to evaluate effects of the PPAR-alpha agonists [[4-Chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio]acetic acid (WY14643) and methyl oleoylethanolamide (methOEA; a long-lasting form of OEA) on 1) nicotine self-administration in rats and squirrel monkeys; 2) reinstatement of nicotine-seeking behavior in rats and monkeys; 3) nicotine discrimination in rats; 4) nicotine-induced electrophysiological activity of ventral tegmental area dopamine neurons in anesthetized rats; and 5) nicotine-induced elevation of dopamine levels in the nucleus accumbens shell of freely moving rats. The PPAR-alpha agonists dose-dependently decreased nicotine self-administration and nicotine-induced reinstatement in rats and monkeys but did not alter food- or cocaine-reinforced operant behavior or the interoceptive effects of nicotine. The PPAR-alpha agonists also dose-dependently decreased nicotine-induced excitation of dopamine neurons in the ventral tegmental area and nicotine-induced elevations of dopamine levels in the nucleus accumbens shell of rats. The ability of WY14643 and methOEA to counteract the behavioral, electrophysiological, and neurochemical effects of nicotine was reversed by the PPAR-alpha antagonist 1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-*a,a*-dimethyl-5-(1-methylethyl)-1*H*-Indole-2-propanoic acid (MK886). These findings indicate that PPAR-alpha might provide a valuable new target for antismoking medications. Mascia P, Pistis M, Justinova Z, Panlilio LV, Luchicchi A, Lecca S., Scherma M, Fratta W, Fadda P, Barnes C, Redhi, G, Yasar S, Le Foll, B, Tanda G, Piomelli D, Goldberg SR. Blockade of nicotine reward and relapse by activation of alpha-type peroxisome proliferator-activated receptors (PPAR- α). *Biological Psychiatry*. 2010; [Epub ahead of

print] PMID: 20801430.

Reinforcing and Neurochemical Effects of Cannabinoid CB1 Receptor Agonists, but not Cocaine, Are Altered by an Adenosine A2A Receptor Antagonist

Several recent studies suggest functional and molecular interactions between striatal adenosine A(2A) and cannabinoid CB(1) receptors. Here, IRP scientists demonstrate that A(2A) receptors selectively modulate reinforcing effects of cannabinoids. They studied effects of A(2A) receptor blockade on the reinforcing effects of delta-9-tetrahydrocannabinol (THC) and the endogenous CB(1) receptor ligand anandamide under a fixed-ratio schedule of intravenous drug injection in squirrel monkeys. A low dose of the selective adenosine A(2A) receptor mg/kg) caused downward shifts of THC and anandamide antagonist MSX-3 (1 mg/kg) shifted THC dose-response curves. In contrast, a higher dose of MSX-3 (3 and anandamide dose-response curves to the left. MSX-3 did not modify cocaine or food pellet self-administration. Also, MSX-3 neither promoted reinstatement of extinguished drug-seeking behavior nor altered reinstatement of drug-seeking behavior by non-contingent priming injections of THC. Finally, using in vivo microdialysis in freely-moving rats, a behaviorally active dose of MSX-3 significantly counteracted THC-induced, but not cocaine-induced, increases in extracellular dopamine levels in the nucleus accumbens shell. The significant and selective results obtained with the lower dose of MSX-3 suggest that adenosine A(2A) antagonists acting preferentially at presynaptic A(2A) receptors might selectively reduce reinforcing effects of cannabinoids that lead to their abuse. However, the appearance of potentiating rather than suppressing effects on cannabinoid reinforcement at the higher dose of MSX-3 would likely preclude the use of such a compound as a medication for cannabis abuse. Adenosine A(2A) antagonists with more selectivity for presynaptic versus postsynaptic receptors could be potential medications for treatment of cannabis abuse. Justinová Z, Ferré S, Redhi GH, Mascia P, Stroik J, Quarta D, Yasar S, MYller CE, Franco R, Goldberg SR. Reinforcing and neurochemical effects of cannabinoid CB1 receptor agonists, but not cocaine, are altered by an adenosine A2A receptor antagonist. *Addiction Biology*, 2010 Nov. 4; [Epub ahead of print] PMID: 21054689.

Automatic Recording of Mediating Behavior in Delayed Matching-and Nonmatching-to-Position Procedures in Rats

Delayed matching-to-position and nonmatching-to-position procedures are widely used to model working memory in rodents. Mediating behavior-which enhances performance but is not explicitly required by the task-is generally considered an obstacle to the measurement of memory, but often occurs despite attempts to prevent it. The ubiquitous nature of mediating behavior suggests it might be analogous to rehearsal, an important component of learning and memory in humans. The aim was to study an easily recordable, rehearsal-like mediating response in rats under baseline conditions and after treatment with amnesic drugs [scopolamine (0.1-0.3 mg/kg) and delta-9-tetrahydrocannabinol (THC; 1-5.6 mg/kg)]. Lighted nosepoke holes were used to present position cues and record delayed matching or nonmatching responses. Performance of a distractor task was required to prevent simply waiting at the correct choice, but the nosepoke holes were left accessible during the delay. Each rat trained with the nonmatching task exhibited one of two mediating "strategies" that increased the odds of a correct choice: responding in the to-be-correct hole during the delay or responding in the opposite hole during the delay. Rats trained with the matching task all showed the former strategy. Treatment with scopolamine disrupted performance of the mediating response. Scopolamine and THC both decreased the effectiveness of the mediating response, increasing errors even on trials when the "appropriate" mediating behavior did occur. The procedures and data analysis approach used here provide an objective, automated means of measuring mediating behavior, which might be useful as an animal model of memory rehearsal. Panlilio LV, Yasar S, Thorndike E, Goldberg SR, Schindler CW. Automatic recording of

mediating behavior in delayed matching- and nonmatching-to-position procedures in rats. *Psychopharmacology* (Berl), 2010 Nov 18; Epub ahead of print).

Direct Involvement of Sigma-1 Receptors in the Dopamine D1 Receptor-Mediated Effects of Cocaine

It is well known that cocaine blocks the dopamine transporter. This mechanism should lead to a general increase in dopaminergic neurotransmission, and yet dopamine D(1) receptors (D(1)Rs) play a more significant role in the behavioral effects of cocaine than the other dopamine receptor subtypes. Cocaine also binds to σ -1 receptors, the physiological role of which is largely unknown. In the present study, D(1)R and σ (1)R were found to heteromerize in transfected cells, where cocaine robustly potentiated D(1)R-mediated adenylyl cyclase activation, induced MAPK activation per se and counteracted MAPK activation induced by D(1)R stimulation in a dopamine transporter-independent and σ (1)R-dependent manner. Some of these effects were also demonstrated in murine striatal slices and were absent in σ (1)R KO mice, providing evidence for the existence of σ (1)R-D(1)R heteromers in the brain. Therefore, these results provide a molecular explanation for which D(1)R plays a more significant role in the behavioral effects of cocaine, through σ (1)R-D(1)R heteromerization, and provide a unique perspective toward understanding the molecular basis of cocaine addiction. Navarro G, Moreno E, Aymerich M, Marcellino D, McCormick PJ, Mallol J, Cortés A, Casadó V, Canela EI, Ortiz J, Fuxe K, Lluís C, Ferré S, Franco R. Direct involvement of sigma-1 receptors in the dopamine D1 receptor-mediated effects of cocaine. *Proc Natl Acad Sci U S A*. 2010 Oct 26; 107(43): 18676-18681. Epub 2010 Oct 18.

G Protein-Coupled Receptor Heteromers as New Targets for Drug Development

There is now a significant amount of experimental evidence indicating that G protein-coupled receptor (GPCR) oligomerization, including homo- and heteromerization, is a general phenomenon. Receptor heteromers possess unique biochemical characteristics that are demonstrably different from those of its individual units. These properties include allosteric modulation(s) between units, changes in ligand recognition, G protein-coupling and trafficking. The discovery of GPCR oligomers have been related to the parallel discovery and application of a variety of resonance energy transfer (RET) techniques, such as bioluminescence, fluorescence and sequential RET (BRET, FRET and SRET, respectively), time-resolved FRET (T-FRET) and fluorescence recovery after photobleaching (FRAP) microscopy. However, RET techniques are difficult to implement in native tissues. For receptor heteromers, indirect approaches, such as the determination of a unique biochemical characteristic ("biochemical fingerprint"), permit their identification in native tissues and their use as targets for drug development. Dopamine and opioid receptor heteromers are the focus of intense research which is related to the possible multiple applications of their putative ligands in pathological conditions, which include basal ganglia disorders, schizophrenia and drug addiction. Ferré S, Navarro G, Casadó V, Cortés A, Mallol J, Canela EI, Lluís C, Franco R. G protein-coupled receptor heteromers as new targets for drug development. *Prog Mol Biol Transl Sci*. 2010; 91: 41-52.

Prime Time for G-protein-coupled Receptor Heteromers as Therapeutic Targets for CNS Disorders: The Dopamine D1-D2 Receptor Heteromer

A number of G-protein-coupled receptors (GPCRs) are currently under consideration as potential therapeutic targets for drugs acting in the central nervous system (CNS). Attempts to discover new medications have operated under the assumption that GPCRs are monomers and that a specific drug activates one single receptor coupled to one single signal transduction mechanism. In the neuronal membrane, GPCRs are now known to be arranged into homo- and hetero-oligomers; drugs acting on a single receptor within a specific heteromer context are thought to induce a particular downstream

signaling. However, there is recent evidence showing that heteromer-tailored drugs can be designed that display different affinities for a given receptor depending on the receptor partners contained within the heteromer. It can therefore be predicted that customized drugs targeting a specific receptor heteromer in the CNS might improve safety and efficacy for their therapeutic targets. Finally, it will be important to identify receptor heteromers that are involved in the pathogenesis of diseases, such as the recently discovered dopamine D1-D3 receptor heteromer, which might play a key role in L-DOPA-induced dyskinesia in Parkinson's disease. Ferré S, Lluís C, Lanciego JL, Franco R. Prime time for G-protein-coupled receptor heteromers as therapeutic targets for CNS disorders: the dopamine D1-D3 receptor heteromer. *CNS Neurol Disord Drug Targets*. 2010; Nov 1;9(5): 596-600.

Interactions Between Intracellular Domains as Key Determinants of the Quaternary Structure and Function of Receptor

Heteromers G protein-coupled receptor (GPCR) heteromers are macromolecular complexes with unique functional properties different from those of its individual protomers. Little is known about what determines the quaternary structure of GPCR heteromers resulting in their unique functional properties. In this study, using resonance energy transfer techniques in experiments with mutated receptors, IRP scientists provide for the first time clear evidence for a key role of intracellular domains in the determination of the quaternary structure of GPCR heteromers between adenosine A(2A), cannabinoid CB(1), and dopamine D(2) receptors. In these interactions, arginine-rich epitopes form salt bridges with phosphorylated serine or threonine residues from CK1/2 consensus sites. Each receptor (A(2A), CB(1), and D(2)) was found to include two evolutionarily conserved intracellular domains to establish selective electrostatic interactions with intracellular domains of the other two receptors, indicating that these particular electrostatic interactions constitute a general mechanism for receptor heteromerization. Mutation experiments indicated that the interactions of the intracellular domains of the CB(1) receptor with A(2A) and D(2) receptors are fundamental for the correct formation of the quaternary structure needed for the function (MAPK signaling) of the A(2A)-CB(1)-D(2) receptor heteromers. Analysis of MAPK signaling in striatal slices of CB(1) receptor KO mice and wild-type littermates supported the existence of A(1)-CB(1)-D(2) receptor heteromer in the brain. These findings allowed the authors to propose the first molecular model of the quaternary structure of a receptor heteromultimer. Navarro G, Ferré S, Cordomi A, Moreno E, Mallol J, Casadó V, Cortés A, Hoffmann H, Ortiz J, Canela EI, Lluís C, Pardo L, Franco R, Woods AS. Interactions between intracellular domains as key determinants of the quaternary structure and function of receptor heteromers. *J Biol Chem*. 2010 Aug 27; 285(35):27346-27359. Epub 2010 Jun 18.

Up-Regulation of Striatal Adenosine A(2A) Receptors with Iron Deficiency in Rats: Effects on Locomotion and Cortico-Striatal Neurotransmission

Brain iron deficiency leads to altered dopaminergic function in experimental animals, which can provide a mechanistic explanation for iron deficiency-related human sensory-motor disorders, such as Restless Legs Syndrome (RLS). However, mechanisms linking both conditions have not been determined. Considering the strong modulation exerted by adenosine on dopamine signaling, one connection could involve changes in adenosine receptor expression or function. In the striatum, presynaptic A(2A) receptors are localized in glutamatergic terminals contacting GABAergic dynorphinergic neurons and their function can be analyzed by the ability of A(2A) receptor antagonists to block the motor output induced by cortical electrical stimulation. Postsynaptic A(2A) receptors are localized in the dendritic field of GABAergic enkephalinergic neurons and their function can be analyzed by studying the ability of A(2A) receptor antagonists to produce locomotor activity and to counteract striatal ERK1/2 phosphorylation induced by cortical electrical stimulation. Increased density of striatal A(2A) receptors was found in rats fed

during 3 weeks with an iron-deficient diet during the post-weaning period. In iron-deficient rats, the selective A(2A) receptor antagonist MSX-3, at doses of 1 and 3 mg/kg, was more effective at blocking motor output induced by cortical electrical stimulation (presynaptic A(2A) receptor-mediated effect) and at enhancing locomotor activation and blocking striatal ERK phosphorylation induced by cortical electrical stimulation (postsynaptic A(2A) receptor-mediated effects). These results indicate that brain iron deficiency induces a functional up-regulation of both striatal pre- and postsynaptic A(2A) receptor, which could be involved in sensory-motor disorders associated with iron deficiency such as RLS. Quiroz C, Pearson V, Gulyani S, Allen R, Earley C, Ferré S. Up-regulation of striatal adenosine A(2A) receptors with iron deficiency in rats: effects on locomotion and cortico-striatal neurotransmission. *Exp Neurol*. 2010 Jul; 224(1): 292-298. Epub 2010 Apr 10.

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Program Activities

New NIDA PAs and RFAs

On September 23, 2010, NIDA issued a Program Announcement (PA) entitled **Pre-Application for the 2011 NIDA Avant-Garde Award Program for HIV/AIDS Research (X02) PAR-10-287**. The NIDA Avant-Garde Award Program for HIV/AIDS Research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose high-impact research that will open new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative—open new areas of research or lead to new avenues of treatment and prevention for HIV/AIDS among drug abusers. The proposed research should reflect ideas substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans-NIH Plan for HIV-Related Research.

<http://www.oar.nih.gov/strategicplan/fy2011/index.asp> The 2011 Avant-Garde Award competition will proceed in two phases. The X02 pre-application is the first phase. X02 pre-applications will be reviewed by external reviewers to identify the most outstanding applications (applications from individuals of exceptional creativity who propose highly significant and innovative projects that are not appropriate for traditional grant mechanisms). Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full applications under RFA-DA-11-002. All awards will be made under RFA-DA-11-002. No awards will be made under this announcement. For additional information, consult the FAQs at <http://drugabuse.gov/avgp.html>. This FOA will utilize the X02 mechanism for submission and consideration of pre-applications. Pre-applications are a necessary first step in applying for a 2011 Avant-Garde Award.

On September 23, 2010, NIDA issued an RFA entitled **2011 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-11-002**. The NIDA Avant-Garde Award Program for HIV/AIDS Research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose high-impact research that will open new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative—open new areas of research or lead to new avenues of treatment and prevention for HIV/AIDS among drug abusers. The proposed research should reflect ideas substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans -- NIH Plan for HIV-Related Research <http://www.oar.nih.gov/strategicplan/fy2011/index.asp>. The 2011 Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-10-287. Pre-applications will be evaluated by a group of external reviewers. Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full applications under this FOA (DP1). The 2011 Avant-Garde awardees will be selected from this group of applicants. This FOA will utilize the DP1 grant mechanism. Pre-applications for 2011 Avant-Garde Awards were solicited under PAR-10-287.

On November 9, 2010, NIDA issued a PA entitled **Molecular Genetics of Drug Addiction and Related Co-Morbidities (R01) PA-11-026**. This FOA is a continuation of the program initiated by RFA-DA-99-003, PA-00-115, PA-03-155, and PA-17-073 "Genetics of Drug Addiction Vulnerability," <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-99-003.html>. For additional NIDA funding opportunities in genetics, refer to the NIDA genetics workgroup homepage:

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<http://www.nida.nih.gov/about/organization/Genetics/GeneticsHome.html>. This FOA seeks investigator-initiated applications for genetic and genomic research projects that identify chromosomal loci and/or genetic variation and haplotypes that are associated with either increased or decreased vulnerability to drug addiction, including stimulants (e.g., cocaine, amphetamine, caffeine), narcotics (e.g. opiates), nicotine/tobacco products, benzodiazepines, barbiturates, cannabis, hallucinogens, and/or multiple drugs of abuse and, as needed, accounting for associated co-morbidities (e.g., HIV/AIDS, major depression, schizophrenia, bipolar disorder, alcoholism) in human beings or animal models.

On November 10, 2010, NIDA issued a PA entitled **The Development of Frontal Cortex And Limbic System And Their Roles In Drug Abuse (R01) PA-11-027**. This funding opportunity announcement (FOA) encourages research project (R01) grant applications to study the development of the frontal and prefrontal cortices which, together with the subcortical areas of the limbic system, play significant roles in mediating emotional and motivated behavior. The proper development of these forebrain and midbrain regions is essential for formation of the neuronal pathways that mediate a number of important functions, including learning and memory, cognition and decision making, the hedonic properties of food and sex, as well as the rewarding properties of drugs of abuse. Furthermore, the development of these complex neural circuits occurs over a wide developmental period from early embryogenesis through late adolescence. Elucidation of the molecular and cellular processes underlying the development of these cortical areas and the limbic system will provide critical insights into the adaptive processes associated with drug addiction as well as insights into mechanisms that might underlie increased vulnerability to drug addiction and co-morbid mental disorders. This initiative is designed to support basic neuroscience research into the fundamental mechanisms of development of the frontal and prefrontal cortices, and the midbrain and basal forebrain structures that mediate the euphoric properties of drugs, as well as understanding how the exposure to drugs of abuse affects the cellular and molecular mechanisms underlying nervous system development of circuits relevant to drug reward and addiction. Vertebrate model systems (such as rat, mouse, chick, frog, zebrafish and non-human primates) and invertebrate systems (such as *Drosophila* and *C. elegans*) provide unique insights into mechanisms of development and are also likely to provide new information about the formation and specification of prefrontal and frontal cortices and the limbic system. Approaches using these or other model systems both in vitro and in vivo are highly relevant to this program announcement. In addition, investigators are encouraged to analyze developmental mechanisms that contribute to sexual dimorphisms in drug addiction and in certain psychiatric disorders relevant to drug abuse and addiction.

On November 16, 2010, NIDA issued a PA entitled **Functional Genetics, Epigenetics, and Non-coding RNAs in Drug Addiction (R01) PA-11-033**. Genetic and genomic studies have identified genes and gene variants that potentially modulate the fundamental biological mechanisms underpinning addictive processes. Discovery of these genes/variants, while extremely valuable, is only a first step in understanding molecular mechanisms of addiction. This FOA encourages basic functional genomic research in two areas: 1. functional validation to determine which candidate genes/variants/epigenetic/non-coding RNA features have an authentic role in addictive processes, and 2. detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. This FOA will utilize the R01 mechanism and runs in parallel with FOAs of identical scientific scope, PA-11-034, that encourages applications under the R21 mechanism and PA-11-035 that encourages applications under the R03 mechanism.

On November 16, 2010, NIDA issued a PA entitled **Functional Genetics, Epigenetics, and Non-coding RNAs in Drug Addiction (R21) PA-11-034**. Genetic and genomic studies have identified genes and gene variants that potentially modulate the fundamental biological mechanisms underpinning addictive processes. Discovery of these genes/variants, while extremely valuable, is only a first step in understanding molecular mechanisms of addiction. This Funding Opportunity Announcement encourages basic functional genomic research in two areas: 1. functional validation to determine which candidate genes/variants/epigenetic/non-coding RNA features have an authentic role in addictive processes, and 2. detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. This FOA will use the NIH Exploratory/Developmental (R21) award mechanism and runs in parallel with FOAs of identical scientific scope, PA-11-033, that encourages applications under the R01 mechanism and PA-11-035 that encourages applications

under the R03 mechanism.

On November 16, 2010, NIDA issued a PA entitled **Functional Genetics, Epigenetics, and Non-coding RNAs in Drug Addiction (R03) PA-11-035**. Genetic and genomic studies have identified genes and gene variants that potentially modulate the fundamental biological mechanisms underpinning addictive processes. Discovery of these genes/variants, while extremely valuable, is only a first step in understanding molecular mechanisms of addiction. This Funding Opportunity Announcement encourages basic functional genomic research in two areas: 1. functional validation to determine which candidate genes/variants/epigenetic/ non-coding RNA features have an authentic role in addictive processes, and 2. detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. This FOA will utilize the NIH Small Research Grant (R03) award mechanism and runs in parallel with FOAs of identical scientific scope, PA-11-033, that encourages applications under the R01 mechanism and PA-11-034 that encourages applications under the R21 mechanism.

On December 6, 2010, NIDA issued a PA entitled **Diversity-promoting Institutions Drug Abuse Research Program (DIDARP) (R24) PAR-11-060**. This FOA encourages Resource-Related Research Project Grant (R24) applications from institutions that serve economically disadvantaged students and communities. Applications should propose to develop or strengthen the drug abuse research infrastructure at the institution and foster the research career development of a diverse cadre of faculty, students and staff who are currently underrepresented in drug abuse research. This FOA will utilize the Resource-Related Research Projects (R24) grant mechanism.

On September 16, 2010, NIDA issued an RFA entitled **Assay Development for High Throughput Screening for Nicotinic Receptor Subunits (R21) RFA-DA-11-007**. The purpose of this FOA is to solicit applications that propose to develop biological assays that will facilitate the discovery of new molecular probes for investigating the biological function of neuronal nicotinic acetylcholine receptors (nAChRs). Membrane-spanning subunits (alpha and beta) aggregate in pentamers to form various combinations of functional nAChR ion channels. Genetic association studies have implicated variants in the $\alpha 5$ - $\alpha 3$ - $\beta 4$ cholinergic nicotinic receptor subunit gene cluster on chromosome 15q24-25.1 for the risk of nicotine addiction, tobacco dependence, smoking, and lung cancer. Other studies have implicated the $\alpha 6$ -subunit in nicotine addiction. This FOA seeks applications proposing to develop biological assays for constitutive receptor combinations involving $\alpha 3$, $\alpha 5$, $\alpha 6$, and/or $\beta 4$ subunits, suitable ultimately for configuration as high throughput screening (HTS) assays. Once developed, these HTS-ready assays can, and will be expected to be, submitted for screening (<http://grants.nih.gov/grants/guide/notice-files/NOT-RM-09-011.html>) by the National Institutes of Health (NIH) Molecular Libraries Production Centers Network (MLPCN) to identify biologically active compounds in a large library of small molecule chemical structures. The chemical structures uncovered through development and use of these assays could then be used for selective ligand development and as possible lead molecules to guide drug discovery in the development of tobacco smoking cessation medications. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism with modifications.

On October 29, 2010, NIDA issued an RFA entitled **Medical Marijuana Policy Research: Exploring Trends and Impacts (R01) RFA-DA-11-008**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations that propose research on medical marijuana-related "quasi-natural experiments" in the US to understand the effects of changing local laws, regulations and policies on the epidemiology of cannabis or other drug and alcohol use including the use of tobacco. These quasi-natural experiments may utilize a community or other population-level law, regulation, or public policy intervention that affects medical marijuana use (i.e. decriminalization, etc.). To address this objective, applicants should propose research studies that will assess social, behavioral, and public health impacts of medical marijuana use and policies. The results of research supported by this FOA are expected to provide critical epidemiologic and evaluation data to inform local, regional, and national public policy and public health research relevant to marijuana use across the Nation.

On December 22, 2010, NIDA issued an RFA entitled **New Molecular Entities to Treat Substance Use Disorders (R01) RFA-DA-12-001**. Through this RFA, NIDA is soliciting grant (R01) applications for preclinical research projects that can be conducted with accelerated pace from the drug discovery stage to the early

development stage, with the ultimate goal of identifying new molecular entities (NME) as candidate compounds and moving them closer to gaining FDA approval of safe and efficacious medications for the treatment of substance use disorders (SUDs).

PAs/RFAs Issued with Other NIH Components/Agencies

On September 15, 2010, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Limited Competition for the Global Research Initiative Program, titled Behavioral/Social Sciences (R01) PAR-10-280**. This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R01) applications from institutions/ organizations that propose to conduct behavioral and social sciences research relevant to global health. This program is intended to promote productive development of foreign investigators from low- and middle-income countries (LMICs), trained in the U.S. or in their home countries through an eligible NIH funded research or research training grant/award. It is expected that this program will stimulate research on a wide variety of high priority health-related issues in those countries, and to advance NIH efforts to address important global health issues. This FOA will utilize the NIH Research Project (R01) grant mechanism.

On October 14, 2010, NIDA, in collaboration with several other NIH components, issued a PA entitled **Translational Scholar Career Awards in Pharmacogenomics and Personalized Medicine (K23) PA-11-009**. The purpose of this Mentored Patient-Oriented Research Career Development Award (K23) is to provide salary and "protected time" (up to five years for this award) to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. Each Research Career Development Award must be tailored to meet the individual needs of the candidate. The Translational Scholar Awards in Pharmacogenomics and Personalized Medicine program is intended to address the scarcity of investigators cross-trained in both clinical research core competencies and modern methods required to address pharmacogenomics research problems in patient populations. Dual mentors from the Clinical and Translational Science Awards consortium and the Pharmacogenomics Research Network are required. This FOA will utilize the NIH Research Career Development Award K23 award mechanism.

On October 19, 2010, NIDA and NIAAA jointly issued a PA entitled **Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R01) PA-11-006**. This FOA is intended to stimulate model-driven research to understand the ways that people make decisions about engaging in behaviors that impact the risk of acquiring or transmitting HIV, or to adhere to treatments for HIV. Decision making processes may contribute to both substance use/abuse and other HIV acquisition or transmission risks. A better understanding of decision making processes in the context of brain neural networks and their associated functions would lead to the development of better strategies to reduce the frequency of HIV-risk behaviors. Therefore, this FOA encourages applications to study 1) cognitive, motivational or emotional mechanisms and/or 2) brain neuroendocrine and reinforcement systems that related to HIV-risk behaviors or treatment non-compliance. Interdisciplinary studies that incorporate approaches from psychology, economics, anthropology, sociology, decision sciences, neuroscience and computational modeling are encouraged. This FOA for R01 applications solicits empirical, hypothesis-driven, confirmatory research and modeling approaches. Exploratory, descriptive or hypothesis-generating research are more appropriate for the complementary FOA's using the R21 or R03 mechanisms. In no cases, should research involving animals be proposed. Such research would be considered non-responsive to this or the companion R21 and R03 FOAs. This FOA will utilize the R01 grant mechanism and runs in parallel with FOAs of identical scientific scope, PA-11-007, that encourages applications under the R21 mechanism and PA-11-008 that encourages applications under the R03 mechanism.

On October 19, 2010, NIDA and NIAAA jointly issued a PA entitled **Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R21) PA-11-007**. This FOA for R21 applications encourages exploratory, descriptive or hypothesis-generating research to understand the ways that people make decisions about engaging in behaviors that impact the risk of acquiring or transmitting HIV, or to adhere to treatments for HIV. Decision making processes may contribute to both substance use/abuse and other HIV acquisition or transmission risks. A better understanding of decision making processes in the context of brain neural networks and their associated functions would lead to the development of better strategies to reduce the frequency of HIV-risk behaviors. Therefore, this FOA encourages applications to study 1) cognitive, motivational or emotional mechanisms and/or 2) brain neuroendocrine and reinforcement systems that related to HIV-risk behaviors or treatment non-

compliance. Interdisciplinary studies that incorporate approaches from psychology, economics, anthropology, sociology, decision sciences, neuroscience and computational modeling are encouraged. In no cases, should research involving animals be proposed. Such research would be considered non-responsive to this or the companion R01 and R03 FOAs. This FOA will use the NIH Exploratory/Developmental (R21) award mechanism and runs in parallel with FOAs of identical scientific scope, PA-11-006, that encourages applications under the R01 and PA-11-008 that encourages applications under the R03 mechanism.

On October 19, 2010, NIDA and NIAAA jointly issued a PA entitled **Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R03) PA-11-008**. This Funding Opportunity Announcement (FOA) encourages applications to understand the ways that people make decisions about engaging in behaviors that impact the risk of acquiring or transmitting HIV, or to adhere to treatments for HIV. Decision making processes may contribute to both substance use/abuse and other HIV acquisition or transmission risks. A better understanding of decision making processes in the context of brain neural networks and their associated functions would lead to the development of better strategies to reduce the frequency of HIV-risk behaviors. Therefore, this FOA encourages applications to study 1) cognitive, motivational or emotional mechanisms and/or 2) brain neuroendocrine and reinforcement systems that related to HIV-risk behaviors or treatment non-compliance. Interdisciplinary studies that incorporate approaches from psychology, economics, anthropology, sociology, decision sciences, neuroscience and computational modeling are encouraged. This FOA for R03 applications is intended to support pilot and feasibility studies; small, self-contained research projects; development of research methodology; and development of new research technology that can be carried out in a short period of time with limited resources. In no cases, should research involving animals be proposed. Such research would be considered non-responsive to this or the companion R21 and R01 FOAs. This FOA will utilize the NIH Small Research Grant (R03) award and runs in parallel with FOAs of identical scientific scope, PA-11-006, that encourages applications under the R01 mechanisms and PA-11-007 that encourages applications under the R21 mechanism.

On October 25, 2010, NIDA, in collaboration with several other NIH components, issued a PA entitled **HIV Infection of the Central Nervous System (R01) PA-11-014**. Through this FOA, participating NIH Institutes invite research grant applications focused on defining the pathogenic mechanisms involved in Human Immunodeficiency Virus (HIV)-1 Associated Neurocognitive Disorders (HAND) and, identifying therapeutic strategies to treat and prevent the neurobehavioral and neurological effects of HIV-1 on the central nervous system (CNS). Applications ranging from basic research to clinical diagnosis and treatment in domestic and international settings are of interest. Multidisciplinary research teams and collaborative alliances are encouraged but not required.

On November 12, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Continued Development and Maintenance of Software (R01) PAR-11-028**. Biomedical research laboratories increasingly undertake a software development project to solve a problem of interest specifically related to that laboratory. These software packages sometimes become useful to a much broader community of users that can include translational and clinical researchers. The goal of this program announcement is to support the continued development, maintenance, testing and evaluation of existing software. The proposed work should apply best practices and proven methods for software design, construction, and implementation to extend the applicability of existing biomedical informatics/computational biology software to a broader biomedical research community. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On November 12, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Brain Disorders in the Developing World: Research Across the Lifespan (R21) PAR-11-031**. The collaborative research programs are expected to 1) conduct research on nervous system development, function and impairment at any stage of life and on topics particularly relevant to LMICs and 2) build research capacity among the LMIC partners and institutions involved in the specific research project. Both immediate objectives will contribute to the long-term goals of building sustainable research capacity in LMICs to initiate and conduct such research, ultimately leading to development of successful treatment and prevention strategies. The R21 grant will provide support to assess needs, to initiate preliminary studies and training, and to organize, plan, prepare, and assemble the information and data for an application for a more comprehensive R01 application involving collaboration between the HIC and LMIC investigators.

On November 12, 2010, NIDA, in collaborations with numerous other NIH components, issued a PA entitled **Methods and Approaches for Detection of Gene-Environment Interactions in Human Disease (R21) PAR-11-032**. The overall goal of this FOA is to develop and test innovative statistical, analytical, and bioinformatics methods and approaches for identifying gene-environment interactions for complex human diseases. Although gene-environment (G x E) interaction can be described in a variety of ways, for the purposes of this FOA, it is defined as any joint effect of one or more genes with one or more environmental factors or exposures that cannot be easily explained by their separate marginal effects. The objectives of this FOA are to further advance the understanding of gene-environment interplay in complex human disease by supporting the further development of analytical methods and tools for gene-environment studies to the field of environmental health sciences. The long-term goal of this initiative is to help identify individuals at highest risk for developing a specific disease or dysfunction based on both their exposure patterns and genetic risk profiles and inform potential environmental modifications or behavioral change interventions that could be implemented to prevent or reduce disease burden.

On November 17, 2010, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Limited Competition: Fogarty International Research Collaboration-Behavioral and Social Sciences (FIRCA-BSS) Research Award (R03) PAR-11-036**. The Fogarty International Center is dedicated to advancing the mission of the National Institutes of Health by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the U.S. and abroad, and training the next generation of scientists to address global health needs. This FOA contributes to the FIC mission, by strengthening research collaborations between NIH funded scientists and scientists in Low-and Middle-Income Countries (LMICs), particularly those with the least economic resources. This FOA responds to a number of goals in the new FIC strategic plan (<http://www.fic.nih.gov/about/pages/strategic-plan.aspx>). The main objectives of the FIRCA program are to: (1) support collaborative efforts in behavioral and social sciences research between NIH-funded scientists and LMIC scientists (referred to as the "LMIC collaborator/ PD/PI") on research of high scientific merit, relevant to global health and of mutual interest and benefit; (2) help achieve Fogarty International Center's strategic plan goals including implementation science, chronic disease, infectious diseases (non-AIDS) and, maternal and child health including the Global Health Initiative (<http://www.theglobalhealthinitiative.org/>); and (3) help build research capabilities and foster further sustained and productive research and research collaborations at the LMIC institution.

On November 17, 2010, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Limited Competition: Fogarty International Research Collaboration - Basic Biomedical (FIRCA-BB) Research Award (R03) PAR-11-037**. The Fogarty International Center is dedicated to advancing the mission of the National Institutes of Health by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the U.S. and abroad, and training the next generation of scientists to address global health needs. This FOA contributes to the FIC mission, by strengthening research collaborations between NIH funded scientists and scientists in Low-and Middle-Income Countries (LMICs), particularly those with the least economic resources. This FOA responds to a number of goals in the new FIC strategic plan (<http://www.fic.nih.gov/about/pages/strategic-plan.aspx>) The main objectives of the FIRCA program are to: (1) support collaborative efforts in behavioral and social sciences research between NIH-funded scientists and LMIC scientists (referred to as the "LMIC collaborator/PD/PI") on research of high scientific merit, relevant to global health and of mutual interest and benefit; (2) help achieve Fogarty International Center's strategic plan goals including implementation science, chronic disease, infectious diseases (non-AIDS) and, maternal and child health including the Global Health Initiative (<http://www.theglobalhealthinitiative.org/>); and (3) help build research capabilities and foster further sustained and productive research and research collaborations at the LMIC institution.

On November 30, 2010, NIDA and NIAAA jointly issued a PA entitled **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R01) PA-11-047**. The purpose of this FOA is to advance research on male-females differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model studies are sought.

On November 30, 2010, NIDA and NIAAA jointly issued a PA entitled **Women and**

Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R21) PA-11-048. The purpose of this FOA is to advance research on male-females differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model studies are sought.

On November 30, 2010, NIDA and NIAAA jointly issued a PA entitled **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R03) PA-11-049.** The purpose of this is to advance research on male-females differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model studies are sought.

On December 7, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Translating Basic Behavioral and Social Science Discoveries into Interventions to Improve Health-Related Behaviors (R01) PA-11-063.** This funding opportunity announcement (FOA) seeks highly innovative Research Project Grant (R01) applications that propose to translate findings from basic research on human behavior into effective clinical, community, or population-based behavioral interventions to improve health. Specifically, this FOA will support interdisciplinary teams of basic and applied biological, behavioral and/or social science researchers in developing and refining novel behavioral interventions with high potential impact to improve health-promoting behaviors (e.g., healthy dietary intake, sun safety, physical activity, or adherence to medical regimens), and/or reduce problem health behaviors (e.g., smoking, tanning or physical activity or alcohol or substance use, abuse or dependence).

On September 10, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Knockout Mouse Phenotyping (U54) RFA-RM-10-011.** The purpose of this FOA issued by the Office of Strategic Coordination, Office of the Director, NIH, is to solicit grant applications from institutions/organizations that propose to perform broad phenotyping of the International Knockout Mouse Consortium's (IKMC) mutant mice. The overall objective of this FOA is to produce functional information for each protein-coding gene in the mammalian genome. This FOA will utilize the U54 award mechanism and runs in parallel with two additional FOAs that solicit applications under the U54 and U42 award mechanisms (RFA-RM-10-012, RFA-RM-10-013).

On September 10, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Knockout Mouse Phenotyping Project Database (U54) RFA-RM-10-012.** The purpose of this FOA issued by the Office of Strategic Coordination, Office of the Director, National Institutes of Health, solicits grant applications from institutions/organizations that propose to develop and implement a Data Coordination Center and Database (DCCDB) as part of the Knockout Mouse Phenotyping Project (KOMP2). The DCCDB will be funded primarily to develop, house, and maintain databases to track the progress of the pipelines for producing the knockout mice from ES cells, collect all phenotype data generated at the phenotyping centers, coordinate these efforts with the International Mouse Phenotyping Consortium (IMPC) and to deliver this information to the members of the KOMP2 research network, NIH staff, and the public via a single integrated web portal of phenotype data. This FOA will utilize the U54 award mechanism and runs in parallel with two additional FOAs that solicit applications under the U54 and U42 award mechanisms (RFA-RM-10-011 and RFA-RM-10-013).

On September 14, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-term Interdisciplinary Research Education Program for New Investigators (R25) RFA-NR-11-002.** This funding opportunity announcement (FOA) issued by the National Institute of Nursing Research (NINR) as part of the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) solicits short-term R25 Research Education Project applications that will focus on providing creative and innovative education research experiences for new scientists in basic behavioral and social science research (b-BSSR). The goal of this initiative is to support the growth of a cohort of scientists with research expertise in b-BSSR to further the understanding of fundamental mechanisms and patterns of behavioral and social functioning relevant to the health and well-being of individuals and populations. This FOA will use the NIH Research Education (R25) grant mechanism. Research education programs may not be transferred from one institution to another, unless strongly justified (see Section VI.2).

On September 28, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Training in Computational Neuroscience: From Biology to Model and Back Again (T90/R90) RFA-DA-11-005.** This

Funding Opportunity Announcement (FOA) is an initiative of the NIH Blueprint for Neuroscience Research (<http://neuroscienceblueprint.nih.gov>), a trans-NIH partnership to accelerate neuroscience research. Sixteen Institutes and Centers (ICs) are participating in the Neuroscience Blueprint. Awards will be administered by the National Institute on Drug Abuse (NIDA) on behalf of the Neuroscience Blueprint. This FOA will support integrated research education and research training programs that provide interdisciplinary training in basic neuroscience and the theoretical and technological approaches of computational neuroscience. This FOA will use the T90 mechanism that includes linked research education and research training programs. Applicants will submit a single unified grant application and if selected for funding, two separate awards will be issued, an R90-research education award and a T90-research training award, based on distinct research education and research training-related funding authorities.

On October 1, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Training in Neuroimaging: Integrating First Principles and Applications (T90/R90) RFA-DA-11-006**. This FOA is an initiative of the NIH Blueprint for Neuroscience Research (<http://neuroscienceblueprint.nih.gov>), a trans-NIH partnership to accelerate neuroscience research. Sixteen Institutes and Centers (ICs) are participating in the Blueprint. This funding opportunity will enable the development of novel, interdisciplinary training programs that integrate comprehensive training in basic neuroscience, the physical and biological bases of neuroimaging, the technologies of in vivo neuroimaging, and the application of these technologies to understanding questions in neuroscience across the life span. Each training program must have two components: a) a pre-doctoral NRSA institutional training program (T90) and b) a short-term research education program (R90) that may include scientists at any stage of the career continuum who are interested in neuroimaging. Programs may also include a full-time non-NRSA institutional pre-doctoral training component (R90). An external advisory committee, a dissemination plan, and an evaluation plan are required. This funding opportunity will use the T90/R90 mechanism that includes linked research training and research education programs. Applicants will submit a single, unified grant application and, if selected for funding, two separate awards will be issued, a T90 (research training award) and a R90 (research education award) based on distinct research training and research education-related funding authorities.

On November 10, 2010, NIDA and NIAAA jointly issued an RFA entitled **Support Opportunity for Addiction Research (SOAR) for New Investigators (R03) RFA-DA-11-010**. Through this FOA, NIDA and NIAAA are interested in receiving applications to supplement new investigators who have, or have a commitment of support to conduct research in basic or clinical alcohol or drug abuse research from funding sources other than NIH (e.g. private foundation). In addition, those applicants currently supported to conduct research on psychiatric disorders that are often found to be co-morbid with substance abuse, are also eligible to apply to SOAR for the purpose of adding a substance or alcohol abuse research component to their on-going research. It is hoped that the SOAR program will facilitate ongoing supported substance abuse and co-morbidity research among entry-level new investigators. The primary goal of the SOAR program is to leverage existing research support in order to strengthen, and possibly expand new investigator's ongoing alcohol, drug abuse and co-morbidity research. It is anticipated that this research program will further assist new investigators in the development of an independent research program in the substance abuse field.

On November 24, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-term Mentored Career Development Awards in the Basic Behavioral and Social Sciences for Mid-career and Senior Investigators (K18) RFA-DE-11-003**. This FOA, issued by the NIH Basic Behavioral and Social Science Opportunity Network (OppNet), invites applications for short-term mentored career development (K18) awards of up to 1 year duration, aimed at established, mid-career and senior investigators who seek an intense, mentored career development experience which will substantially improve their ability to pursue future research in the basic behavioral and social sciences. The intent of this FOA is to provide candidates with protected time to achieve a shift in the focus of their research direction in the basic behavioral and social sciences, or to substantially enrich a current b-BSSR research program through the introduction of tools, theories or approaches from another discipline or area of science. Two categories of candidates are targeted: (a) biomedical or clinical researchers with little experience in basic behavioral and social sciences research seeking training with a well established b-BSSR investigator in order to explore the introduction of b-BSSR into their research

programs; and (b) investigators in the basic or applied behavioral and social sciences who wish to build new components or domains of b-BSSR into their research programs. Illustrative examples include but are not limited to: a psychologist seeking training in econometrics in order to expand a research program on basic mechanisms of decision-making; a clinical epidemiologist seeking training in social network dynamics to better understand the spread of health behaviors in populations; a demographer seeking training in psychoneuroimmunology in order to understand the mechanisms whereby sociodemographic factors get "under the skin" to impact health disparities; an ethologist seeking training in neuroscience to facilitate examination of how patterns of maternal care result in epigenetic changes in brain regions and brain structure.

On December 2, 2010, NIDA, with other NIH components, participated in the issuance of the omnibus **NIH Summer Research Experience Programs (R25) PAR-11-050**. The purpose of this program is to provide a high quality research experience for high school and college students and for science teachers during the summer academic break. These summer programs are expected to: help attract young students to careers in science; provide opportunities for college students to gain valuable research experience to help prepare them for graduate school; and enhance the skills of science teachers and enable them to more effectively communicate the nature of the scientific process to their students. The programs would also contribute to enhancing overall science literacy.

On December 8, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Blueprint for Neuroscience Research Short Courses in Neurotherapeutics Development (R25) RFA-NS-12-001**. This FOA solicits Research Education Grant (R25) applications to develop and implement short courses on neurotherapeutics development for academic neuroscientists. The short courses should provide participants with a sufficient overview of the neurotherapeutics development process to (1) understand the steps required for therapeutics development, (2) anticipate and overcome common challenges in the process, and (3) interact effectively with collaborators who have expertise in various aspects of therapeutics development. The short courses should primarily target independent academic neuroscience researchers and senior post-doctoral fellows interested in incorporating treatment development into their research programs.

On December 6, 2010 NIDA issued a **Notice of Intent to Publish a Funding Opportunity Announcement titled Grand Opportunity in Medications Development for Substance-Related Disorders (U01)** <http://grants.nih.gov/grants/guide/notice-files/NOT-DA-11-003.html>. The goal is to promote the submission of applications for studies that will accelerate the development of medications for the treatment of Substance-Related Disorders (SRDs). The purpose of the FOA is to fund pivotal medication studies that will have high impact and quickly yield the necessary results to advance medications to FDA approval. These studies will be supported by the U01 cooperative agreement funding mechanism, which will include a significant scientific and programmatic involvement of NIDA staff. Applications for up to 3 years and for a budget of up to \$5 million per year will be acceptable. Program Contact: Ivan Montoya

Other Program Activities

Clinical Trials Network (CTN) Update

RFA: Thirteen applications in response to the RFA DA-10-009, entitled "The National Drug Abuse Treatment Clinical Trials Network (U10)," were awarded on September 1, 2010.

Protocols: A total of 46 protocols have been initiated since 2001, including multi-site clinical trials (32), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 23 ancillary studies have been supported by CTN and non-CTN funds. There are about 11,800 participants enrolled in CTN studies.

Primary outcome papers are published and dissemination materials have been developed with CSAT's ATTC on the following:

- **Protocol CTN 0001**, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification
- **Protocol CTN 0002**, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification
- **Protocol CTN 0005**, MI (Motivational Interviewing) To Improve

Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

- **Protocol CTN 0006**, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics
- **Protocol CTN 0007**, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics
- **Protocol CTN 0010**, Buprenorphine/Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/Young Adults

Primary outcome papers are published or in press for:

- **Protocol CTN 0003**, Bup/Nx: Comparison of Two Taper Schedules
- **Protocol CTN 0004**, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
- **Protocol CTN 0008**, A Baseline for Investigating Diffusion of Innovation
- **Protocol CTN 0009**, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs
- **Protocol CTN 0011**, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities
- **Protocol CTN 0012**, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs
- **Protocol CTN 0013**, Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers
- **Protocol CTN 0015**, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial
- **Protocol CTN 0016**, Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment
- **Protocol CTN 0017**, HIV and HCV Intervention in Drug Treatment Settings
- **Protocol CTN 0018**, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment
- **Protocol CTN 0019**, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment
- **Protocol CTN 0021**, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse. This is the first Spanish-only protocol in the CTN.
- **Protocol CTN 0029**, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with ADHD.
- **Protocol CTN 0030A2**, Effects of Chronic Opioids in Subjects with a History of Opioid Use

In addition, the following protocols have submitted primary paper:

- **Protocol CTN 0014**, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
- **Protocol CTN 0028**, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD)
- **Protocol CTN 0030**, Prescription Opioid Addiction Treatment Study (POATS)
- **Protocol CTN 0032**, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.

The following protocols have locked data:

- **Protocol CTN 0027**, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCD). The clinical phase of

the study is completed; it is in the data analysis phase.

- **Protocol CTN-0027A2**, Retention of Suboxone™ Patients in START: Perspectives of Providers and Patients. The overall purposes of the supplemental study are to identify and assess barriers for retaining Suboxone™ patients. This ancillary study has completed enrollment, the database has been locked, and qualitative data collected from interviews and focus groups with 281 participants (202 patients, 68 staff, 11 Executive/Program Directors) are currently being coded and analyzed using ATLAS.ti. The first draft of the final report has begun.
- **Protocol CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR; it is in the data analysis phase. Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. This total represents 21 more participants than proposed and was reached one week earlier than planned. Data lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol CTN 0031A1**, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Recruitment was completed on September 30, 2009, yielding a total of 173 participants across 6 sites completing the data collection and blood draw procedures. Data lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol CTN 0031A2**, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. It investigates the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA. Data lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol CTN 0031A3**, Organizational and Practitioner Influences on Implementation of STAGE-12. The study assesses the influence of counselor and organizational variables on fidelity of the STAGE-12 intervention during the clinical trial, tests the impact of fidelity on clinical trial participant outcomes, and explores the influence of counselor and organizational variables on sustainability of the STAGE-12 intervention following completion of the clinical trial. Study staff has already collected the organizational and counselor level data from all ten STAGE-12 sites. The baseline data obtained in this research formed the foundation for an R01 grant awarded by DESPR to Joseph Guydish, PhD, at the University of California, San Francisco.

The following protocols have ended new enrollment, and are in the follow-up or data-lock phase:

- **Protocol CTN 0027A1**, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies. This ancillary study consented 843 of the 1,269 subjects from the START study. Data collection is complete and analysis has begun.
- **Protocol CTN 0030A3**, POATS Long-Term Follow Up Study (LTFU) is being conducted at all POATS sites to examine long-term outcomes for individuals who participated in CTN-0030 with opioid analgesic (OA) dependence. This study will follow POATS participants for 42 months after randomization in the POATS study.
- **Protocol CTN 0032A1**, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This is an ancillary study is an assessment of the cost-effectiveness of on-site HIV testing in drug abuse treatment settings vs. referral for off-site testing. The PI is Dr. Bruce Schackman. The project is conducted in collaboration with NIDA's DESPR.
- **Protocol CTN 0033-Ot**, Methamphetamine Use among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. The study is

collaboration among four Nodes: Pacific NW, Southwest, Oregon/Hawaii, and Ohio Valley.

- **Protocol CTN 0034-Ot**, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Pacific Northwest Node.
- **Protocol CTN 0035-Ot**, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the California/Arizona Node.
- **Protocol CTN 0036-Ot**, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.
- **Protocol CTN 0038-Ot**, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders. The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (APIs) and the readiness of substance abuse treatment programs serving APIs to participate in clinical trials and adopt evidence based practices. This study is a collaboration with NIH NCMHD.

The following protocols are currently enrolling:

- **Protocol CTN 0037**, Stimulant Reduction Intervention Using Dosed Exercise (STRIDE). This randomized clinical trial is testing the efficacy of the addition of exercise to treatment as usual in improving drug abuse treatment outcomes in patients abusing stimulants. As of December 9, 2010, 51 participants have been enrolled at four sites. Enrollment will begin at five additional sites in early 2011.
- **Protocol CTN 0044**, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders. The purpose of this study is to evaluate the effectiveness of adding an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus abstinence incentives as an adjunct to community-based, outpatient substance abuse treatment. As of December 8, 2010, 196 randomized participants have been enrolled from 10 sites.
- **Protocol CTN 0046**, Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes. The primary objective of this study is to evaluate the impact of substance abuse treatment as usual plus smoking cessation treatment (TAU+SCT), relative to substance abuse treatment as usual (TAU), on drug abuse outcomes. As of December 8, 2010, 180 randomized participants have been enrolled from 12 sites.
- **Protocol CTN 0047**, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED). The study objective is to evaluate the implementation of, and outcomes associated with, a screening and brief intervention (SBI) process to identify individuals with substance use, abuse, or dependence seen in emergency departments (EDs) and to provide interventions and/or referral to treatment consistent with the severity of their substance use disorder. Training for the two Wave 1 sites took place July 19-21, 2010 in Albuquerque, NM. The first participant was randomized on October 18, 2010 and enrollment stands at 76 as of December 6, 2010. The four Wave 2 sites are: Massachusetts General Hospital (New England Node); Bellevue Hospital Center (Greater New York Node); Jackson Memorial Hospital (Florida Node); and West Virginia University Hospital (Appalachian Tri-State Node). National training was held January 11-14, 2011 in Albuquerque, NM.

The following protocols are in the implementation/development phase:

- **Protocol CTN 0044A2**, Acceptability of a Web-delivered, Evidence-

based, Psychosocial Intervention among Individuals with Substance Use Disorders who Identify as American Indian/Alaska Native. Results from prior research support the efficacy of a web-based version (Therapeutic Education System: TES) of the Community Reinforcement Approach (CRA) with individuals in outpatient substance abuse treatment; however, TES has yet to be tested among American Indian/Alaska Native (AI/AN) populations. The principal objective of this study is to explore the acceptability of TES among a diverse sample of AI/AN enrolled in outpatient substance abuse treatment. The study is currently being implemented in two treatment programs: City / County Alcohol & Drug Programs (CCADP) in Rapid City, SD (Ohio Valley Node) and Native American Rehabilitation Association of the Northwest (NARA) in Portland, OR (Western States Node).

- **Protocol CTN 0045-Ot**, Rates of HIV Testing and Barriers to Testing in African Americans Receiving Substance Abuse Treatment. This is an observational study seeking to: (1) Compare the proportion of African American and non-African Americans receiving treatment at substance abuse treatment clinics that have been tested for HIV within the past 12 months; (2) Observe relationships between rates of African Americans who have not been tested and a) the types of testing offered at substance abuse treatment clinics and b) the types of outreach strategies used to engage persons in HIV testing; and (3) assess African American clients' self-reported barriers to accessing HIV testing, in relation to other ethnicities.
- **Protocol CTN 0048**, Cocaine Use Reduction with Buprenorphine (CURB). The aim of this study is to investigate the safety and efficacy of buprenorphine in the presence of naltrexone for the treatment of cocaine dependence in a sample of individuals who meet criteria for cocaine dependence and lifetime opioid dependence or cocaine dependence and past year opioid abuse. Enrollment is expected to begin in 2011.
- **Protocols CTN 0037A1, CTN-0044A1, CTN0046A1, and CTN0047A1**, Organizational and Practitioner Influences on Patient Outcomes. This series of ancillary studies is assessing associations between site organizational and practitioner variables and site differences in clinical trial outcomes. Protocol CTN 0049, Project HOPE (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users) has been approved to develop into a full protocol. The study will evaluate the effectiveness of a brief intervention, delivered to HIV-infected drug users recruited from the hospital setting, in achieving viral suppression.
- **Protocol CTN 0050**, START Follow-Up Study. This concept has been approved for further development into a protocol. The study will follow participants from the CTN 0027 START (Starting Treatment with Agonist Replacement Therapies) study for 3-5 years to assess longer-term outcomes of buprenorphine/naloxone versus methadone treatment and investigate factors associated with post-START treatment access, utilization, and outcomes.
- **Protocol CTN 0051**, Vivitrol. This study is under development.

In addition to the primary CTN trials, there are currently five secondary analyses underway using data across several of the completed trials. Manuscripts are in progress and/or being prepared by the investigators. Posters are being presented at scientific meetings for several of the trials.

1. Gender Differences in the Prevalence and Predictors of HIV Risk Behaviors, PI: Audrey Brooks (CA/AZ Node) -- paper published by Substance Use and Misuse;
2. Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node); poster at ICTAB, paper published by Journal of Substance Abuse Treatment, Manuscript submitted to special issue of AJDAA.
3. The relationships between demographic characteristics of patients and therapists, measures of therapeutic process and therapeutic alliance, and outcomes, PIs: Alyssa Forcehimes (Southwest Node) and Kathleen Burlew (Ohio Valley Node); poster at CPDD, Manuscript submitted to special issue of AJDAA.
4. The Efficacy of Motivational Enhancement Therapy for African Americans, PI: Kathleen Burlew (Ohio Valley Node); poster at CPDD, Manuscript submitted to

special issue of AJDAA.

5. Substance Abuse Treatment Outcomes in Racial/Ethnic Minority Populations, PI: Carmen Masson (California-Arizona Node).

There are also approximately 45 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since May 2010

Al'Absi, Mustafa N. -- University of Minnesota Twin Cities
Stress, Appetite, and Smoking Relapse

Altice, Frederick Lewis -- Yale University
HIV, Buprenorphine, and the Criminal Justice System

Andersen, Susan L. -- McLean Hospital (Belmont, MA)
Sensitive Periods, Development, and Substance Abuse

Anderson, Beth Marie -- Hartford Hospital
Effects of Marijuana on Driving: A Standardized Assessment

Bailey, William C. -- University of Alabama at Birmingham
Web-Based Smoking Cessation Intervention: Transition From Inpatient to Outpatient

Bajic, Dusica -- Children's Hospital Boston
Age Differences of Brain Circuits Mediating Morphine Effect & Morphine Tolerance

Beckwith, Curt G. -- Miriam Hospital
CARE Corrections: Technology for Jail HIV/HCV Testing, Linkage, and Care (TLC)

Beguín, Cecile -- McLean Hospital (Belmont, MA)
Kappa Opioid Antagonists: Synthesis, Potency, Selectivity, and Time-Course

Bell, Morris D. -- Yale University
Cognitive Remediation and Work Therapy in the Initial Phase of Substance Abuse

Bergman, Jack -- McLean Hospital (Belmont, MA)
Candidate Medications for Cannabis Addiction: FAAH Inhibitors

Blosnich, John Rudolph -- West Virginia University
Risk Factors Related to Smoking Disparities Among Sexual Minority Young Adults

Bluthenthal, Ricky N. -- University of Southern California
Exploratory Research on Late Initiation of Drug Injection

Booth, Raymond G. -- University of Florida
Novel Functionally-Selective Serotonin 5HT₂ Drugs for Amphetamines Abuse/Disorder

Booze, Rosemarie M. -- University of South Carolina at Columbia
HIV/Cocaine Neurotoxicity in Females

Branch, Andrea D. -- Mount Sinai School of Medicine
Optimizing Vitamin D Treatment in HIV/AIDS: An RCT

Brimijoin, William Stephen -- Mayo Clinic
Cocaine Hydrolase Gene Therapy for Cocaine Abuse (DPI)

Brook, Judith S. -- New York University School of Medicine
Drug Use and Problem Behaviors in Minority Youth

Brouwer, Kimberly C. -- University of California San Diego
Crossing Borders: HIV and Substance use at the Gateway to North America

Bucci, David J. -- Dartmouth College
Nicotinic Acetylcholine Receptors and Inhibitory Behavior

Cai, Li -- University of California Los Angeles
Measurement of Recovery from Drug Addiction LC

Carrico, Adam Wayne -- University of California San Francisco
A Stress and Coping Model of Stimulant Use Among MSM

- Carroll, Kathleen M.** -- Yale University
Computer-based Training in Cognitive Behavioral Therapy: Web-based delivery of CB
- Caudle, Robert M.** -- University of Florida
Morphine Induced Alterations in NMDA Receptor Subunit Expression
- Chang, Judy C.** -- Magee Women's Research Institute and Foundation
Communication on Illicit Drug and/or Alcohol Use in Obstetrics
- Chawarski, Marek C.** -- Yale University
Naltrexone and Behavioral Drug and HIV Risk Reduction Counseling in Russia
- Chen, Rong** -- University of Michigan at Ann Arbor
Transporter Mechanism of Amphetamine Sensitization
- Clark, Robin E.** -- University of Massachusetts Medical School Worcester
Cost, Benefit & Regulation of Buprenorphine Treatment for Medicaid Beneficiaries
- Cohen, Ronald A.** -- Miriam Hospital
Improving Adherence and Cognition in Substance-Using HIV Patients
- Comer, Sandra D.** -- New York State Psychiatric Institute
Pioglitazone for the Treatment of Opioid and of Nicotine Dependence
- Crano, William D.** -- Claremont Graduate University
Marijuana Prevention Ad Impact: Ad Coding and Secondary Analyses of National Data
- Cunningham, Kathryn A.** -- University of Texas Medical BR Galveston
Inhibitors of 5-HT₂CR Protein: Protein Interactions for Stimulant Pharmacotherapy
- Cunningham, William E.** -- University of California Los Angeles
Effectiveness of Peer Navigation to Link Released HIV+ Jail Inmates to HIV Care
- Dash, Chandranu** -- Meharry Medical College
Cocaine-Induced Epigenetic Changes in CD4+ T cells and HIV-1 Replication
- De Biasi, Mariella** -- Baylor College of Medicine
Genetic Influences Over Nicotine Withdrawal
- Eack, Shaun M.** -- University of Pittsburgh at Pittsburgh
Adapted Cognitive/Affective Remediation for Cannabis Misuse in Schizophrenia
- Eissenberg, Thomas Evan** -- Virginia Commonwealth University
Realtime Waterpipe Tobacco Smoke Toxicant Sampling in the Natural Environment
- Evins, A. Eden** -- Massachusetts General Hospital
Cognitive Remediation with D-cycloserine to Improve Smoking Cessation Outcomes
- Fagan, Abigail Anne** -- University of South Carolina at Columbia
Violent Victimization, Neighborhood Context and Adolescent Drug Use
- Fisher, Dennis G.** -- California State University Long Beach
Behavioral Science Aspects of Rapid Test Acceptance
- Fox, Howard S.** -- University of Nebraska Medical Center
Transcriptional Regulation, the Nuclear Proteome, and HIV/Meth/cART: From Profiling
- Frederick, Blaise Debonneval** -- McLean Hospital (Belmont, MA)
Realtime Near Infrared Spectroscopy of the Frontal Lobe for Neurofeedback
- Fuemmeler, Bernard F.** -- Duke University
Elucidating Links Between ADHD Symptoms and Tobacco/Alcohol Use Trajectories
- Gabuzda, Dana H.** -- Dana-Farber Cancer Institute
Systems Analysis of Inflammatory Pathways in HIV Infection
- Garner, Bryan R.** -- Chestnut Health Systems, Inc.
Impact, Predictors, and Mediators of Therapist Turnover
- Garofalo, Robert** -- Children's Memorial Hospital (Chicago)
Text Messaging Intervention to Improve ART Adherence among HIV-positive Youth
- Gilbert, David G.** -- Southern Illinois University Carbondale
Nicotine for Marijuana Withdrawal
- Goeders, Nicholas E.** -- Louisiana State University HSCS Shreveport

Cocaine Addiction Medication EMB-001

Goodenow, Maureen M. -- University of Florida
Substance Use and Immunity in HIV+ Adolescents by Systems Biology

Gordon, Michael Scott -- Friends Research Institute, Inc.
A Randomized Controlled Trial and Cohort Study of HIV Testing and Linkage to Care

Gottlieb, Jacqueline -- Columbia University Health Sciences
Pavlovian Learning, Attention and Decisions

Gustafson, David H. -- University of Wisconsin Madison
"Community Infrastructure" Grants Program

Haggerty, Kevin P. -- University of Washington
Feasibility of Substance Abuse Prevention in Foster Care Settings

Haney, Margaret -- New York State Psychiatric Institute
Marijuana Relapse: Influence of Tobacco Cessation and Varenicline

Hankins, Gary D. -- University of Texas Medical Br Galveston
Bupropion for Smoking Cessation During Pregnancy

Hauser, Kurt F. -- Virginia Commonwealth University
Mechanisms of Opiate Drug-HIV-Induced Neurodegeneration

Hong, L. Elliot -- University of Maryland Baltimore
Shared Neural Circuitry in Comorbid Schizophrenia and Nicotine Addiction

Islam, Leila Z. -- Virginia Commonwealth University
Using Behavioral Incentives to Promote Exercin Cocaine Dependent Women

Jones, Hendree E. -- Research Triangle Institute
HIV and Drug Use in Georgian Women

Jones, Sara R. -- Wake Forest University Health Sciences
Methylphenidate, Serotonin and Dopamine Interactions

Kalueff, Allan V. -- Tulane University of Louisiana
Developing Adult Zebra fish-Based Models to Study Hallucinogenic Drug Action

Kenny, Paul J. -- Scripps Research Institute
Development of $\alpha 5^$ nAChR Positive Allosteric Modulators for Tobacco Dependence*

Lerman, Caryn -- University of Pennsylvania
Cognitive Training for Nicotine Dependence

Levine, Andrew J. -- University of California Los Angeles
Pathways to HIV-Associated Neurocognitive Disorders: A Systems Biology Approach

Lewis, William -- Emory University
Cocaine HIV/AIDS, and Antiretrovirals

Lowe, Robert A. -- Oregon Health and Science University
Building an Evidence Base for Treating the Vulnerable: A Community Partnership

Mackie, Kenneth P. -- Indiana University Bloomington
Neuronal Cannabinoids

Madras, Bertha K. -- Harvard University (Medical School)
Methamphetamine and Neurodevelopment in Adolescent and Adult Mice

Margolis, Elyssa -- Ernest Gallo Clinic and Research Center
Heterogeneity of Ventral Tegmental Area Neurons and Opioid Reward

Markou, Athina -- University of California San Diego
Development of GABABeta Receptor Compounds for Nicotine Dependence

Marshal, Michael P. -- University of Pittsburgh at Pittsburgh
Substance Use Disparities Among Sexual Minority Girls: A Longitudinal Study

Martin, Laura E. -- University of Kansas Medical Center
Neural Mechanisms Associated with Nicotine Addiction and Obesity Co-Morbidities

Mason, Barbara J. -- Scripps Research Institute
Pharmacological Treatment of Cannabis Withdrawal and Dependence

Matthews, Alicia K. -- University of Illinois at Chicago
Culturally Targeted & Individually Tailored Smoking Cessation Study: LGBT Smokers

Mawhinney-Delson, Samantha M. -- University of Colorado Denver
Sex, Drugs and Consequences of Dropout on HIV Outcomes in WIHS, MACS, and AIEDRP

Milligan, Erin D. -- University of New Mexico Health Sciences Center
Spinal Neuroimmune Mechanisms Underlying IL-10 Gene Therapy for Pain Control

Mintzer, Miriam Z. -- Johns Hopkins University
Effects of Cognitive Training in Methadone Maintenance Patients

Mojtabai, Ramin -- Johns Hopkins University
Treatment Patterns and Barriers in Comorbid Mental and Substance Disorders

Neumaier, John F. -- University of Washington
Striatal 5-HT₆ receptors, Reward and Addiction

Newman, Joseph P. -- University of Wisconsin Madison
Matching Cognitive Remediation to Cognitive Deficits in Substance-Abusing Inmates

Norman, Andrew B. -- University of Cincinnati
A Human Antibody as an Immunotherapy for Cocaine Abuse (DP1)

O'Leary, Daniel S. -- University of Iowa
Marijuana Use and Schizophrenia

Ouellet, Lawrence J. -- University of Illinois at Chicago
Seek, Test, Treat: An Integrated Jail-Prison-Community Model for Illinois

Pears, Katherine C. -- Oregon Social Learning Center, Inc.
Long-Term Effects of a School Readiness Intervention for Foster Children

Pentel, Paul R. -- Minneapolis Medical Research Foundation, Inc.
Preclinical Studies of a Heroin/Morphine Vaccine for Opiate Addiction

Piomelli, Daniele -- University of California Irvine
Optimization and Preclinical Development of FAAH Inhibitors for Smoking Cessation

Pope, Harrison G. -- McLean Hospital (Belmont, MA)
Medical Consequences of Long-Term Anabolic-Androgenic Steroid Abuse

Potula, Raghava -- Temple University
Mechanism of Immune Dysregulation Secondary to Methamphetamine Abuse

Quan, Vu Minh -- Johns Hopkins University
Seek, Test, Treat Strategies for Vietnamese Drug Users: A Random Controlled Trial

Ray, Lara -- University of California Los Angeles
Neuroimaging Probes of Medication Response in Smokers

Rich, Josiah D. -- Miriam Hospital
Improving Linkage to HIV Care Following Release from Incarceration

Rochet, Jean-Christophe -- Purdue University West LaFayette
Mechanisms of DJ-1 Protection Against Methamphetamine Neurotoxicity

Sacks, Stanley -- National Development & Research Institutes
START Together: HIV Testing and Treatment in and after Jail

Salinas, Emilio -- Wake Forest University Health Sciences
CRCNS: Investigating Perceptual Processing Speed and its Impact on Choice Behavior

Schmitz, Joy Marie -- University of Texas Health Science Center Houston
Cognitive-Enhancing DA Medications for Cocaine Dependence

Schuman-Olivier, Zev David -- Massachusetts General Hospital
Effects of Mindfulness Training on Impulsivity & Inhibitory Control in Smokers

Scott, Christy K. -- Chestnut Health Systems, Inc.
Pathways to Recovery: Older Substance Users

Seal, David W. -- Medical College of Wisconsin
Seek, Test, and Treat Strategies

- Shoptaw, Steven** -- University of California Los Angeles
Phase I Safety Interaction Trial of Ibudilast with Methamphetamine
- Silverman, Richard B.** -- Northwestern University
New Inactivators of GABA Aminotransferase for Addiction
- Smith, Stephen M.** -- Oregon Health and Science University
A Novel Cannabinoid Receptor in Cortical Nerve Terminals
- Springer, Sandra Ann** -- Yale University
Naltrexone for Opioid Dependent Released HIV+ Criminal Justice Populations
- Strathdee, Steffanie A.** -- University of California San Diego
Impact of Drug Policy Reform on the HIV Risk Environment among IDUs in Tijuana
- Tucker, Joan S.** -- Rand Corporation
The Role of Peer Networks in Youth Drug Use
- Turncliff, Ryan** -- Alkermes, Inc.
Clinical Advancement of RDC-0313-Buprenorphine: a Novel Approach to Opioid
- Unterwald, Ellen M.** -- Temple University
Cocaine-Induced Opioid, Dopamine & Behavioral Changes
- Verdin, Eric M.** -- J. David Gladstone Institutes
Novel Model for HIV Latency in Primary Memory T Cells
- Waldron, Holly Barrett** -- Oregon Research Institute
Building Outcomes with Observation-Based Supervision: An FFT Effectiveness Trial
- Wang, Jia Bei** -- University of Maryland Baltimore
Development of I-THP as New Medication for Drug Addiction (DP1)
- Wang, Rongfu** -- Baylor College of Medicine
Development of Novel Vaccines for Cocaine Abuse
- Weeks, Margaret R.** -- Institute for Community Research
Translation of the Risk Avoidance Partnership (RAP) for Drug Treatment Clinic
- Wigdahl, Brian** -- Drexel University
High Specificity HIV-1 Markers Predictive of Neuro-AIDS
- Wilhelmsen, Kirk C.** -- University of North Carolina Chapel Hill
Deep Sequencing Studies for Cannabis and Stimulant Dependence
- Williams, Jason** -- Research Triangle Institute
Methods to Compare Mechanisms of Action in Substance Use Programs
- Wilson, Stephen Jeffrey** -- Pennsylvania State University -- University Park
Effects of Smoking Expectancy on the Neural Response to Reward in Human Smokers
- Wohl, David A.** -- University of North Carolina Chapel Hill
RCT of an Augmented Test, Treat, Link, & Retain Model for NC and Texas Prisoners
- Woolverton, William L.** -- University of Mississippi Medical Center
Delay Discounting and the Choice to Take a Drug
- Wu, Li-Tzy T.** -- Duke University
Classification of Substance Use Disorders in Adolescents
- Zhu, Jinmin** -- Massachusetts General Hospital
Methylphenidate, Opioid Receptors and Addiction

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1281 applications, including both primary and dual assignments, for which the Office of Extramural Affairs (OEA) managed the programmatic referral process during this Council cycle. Of these, NIDA received the primary assignment on 813 applications.

OEA arranged and managed 9 grant review meetings in which 128 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA staff arranged and managed 15 contract proposal and concept review meetings.

NIDA has one standing chartered committee, NIDA-K, which reviews Career Development applications and Institutional Training Grant applications (T32). There were also 8 Special Emphasis Panels to review grant applications for a variety of reasons:

- Conflicts with the chartered committee
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Cutting-Edge Basic Research Awards (CEBRA) (R21)
- Science Education and Research Education Programs (R25)
- Multi-site Clinical Trials (R01)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

R&D and non-R&D Contract Reviews

- NO1DA-11-8894 - Statistical Analysis in Support of DPMC Clinical Trial

Phase I SBIR Contract Reviews

- N43DA-11-1206 - International Activities
- N43DA-11-5563 - Developing Implementation Packages for Evidence-based HIV Prevention Intervention Materials for Drug Users
- N43DA-11-5562 - Improving Measures of Addiction
- N43DA-11-5564 - Developing, Validating, Refining Tools for Ecologic Momentary Assessment
- N43DA-11-5566 - Reintegration of Criminal Offenders into the Community
- N43DA-11-5567 - E-Technology Tools for Extending the Reach of Prevention

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International Activities

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Media and Education Activities

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Interventions in Rural and Remote Locations

- N43DA-11-2223 - Development of a Device for Auto-administering Naloxone to Overcome Overdose
- N43DA-11-2222 - Development of an Innovative Electronic Health Record (EHR) Translator Platform Facilitating Communication among Different EHR Systems Used in Clinical Research and Treatment
- N43DA-11-2224 - Development of a Device to Assess Hyperalgesia at the Bed Side by the Cold Pressor Test
- N43DA-11-8897 - Development of New Methods and Approaches to Monitor Medication Compliance in Clinical Trials
- N43DA-11-8898 - New Techniques for the Large Scale Production and Purification of Antibodies or Vaccines for the Treatment of Substance Use Disorders
- N43DA-11-4413 - Real-time Activity as a Potential Diagnostic Marker for Pain or Drug-craving
- N43DA-11-4414 - Video Game Targeting Relapse Prevention in Youth with Substance use Disorders
- N43DA-11-2225 - Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse

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Certificates of Confidentiality

Between August 4, 2010 and December 9, 2010, OEA processed 113 Certificate of Confidentiality applications, including 21 amendments for either extension of expiration date or protocol change.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations that included: QVR Overview and Recent System Enhancements, by Dr. Thor Fjellstedt; What's New in Peer Review at CSR, by Dr. Cheryl Kitt; The NIH Blueprint, by Dr. David Shurtleff; Collaboration and Team Science, by Drs. Howard Gadlin, Michelle Bennett, and Samantha Levine; and Protecting Human Research Subjects, by Drs. Ann Hardy and Maria Stagnitto.

CTN Review Activities

The CTN Data and Safety Monitoring Board(s) met:

- August 27, 2010 to review study protocol CTN 0048: Cocaine Use Reduction with Buprenorphine (CURB)
- September 3, 2010 to review the progress of the GO grant, 5 RC2 DA028973-02, Project AWARE: HIV Testing and Counseling in STD Clinics: an Adaptation of CTN 0032. The study reached its goal and randomized 5,013 participants.
- November 22, 2010 to discuss study protocol CTN 0050, START Long Term Follow up.

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Congressional Affairs (Prepared January 21, 2011)

Appropriations

The President's Fiscal Year 2011 budget request included \$32.1 billion for NIH, a \$1 billion (3.2%) increase over FY 2010. For NIDA, the request included \$1.094 billion, \$34.6 million (3.3%) over the FY 2010 level.

NIH is currently operating under a Continuing Resolution (at the FY 2010 level) that will expire on March 4, 2011.

112th CONGRESS

As a result of the November 2010 elections, Republicans now control the House of Representatives and Democrats continue to control the Senate. The most relevant committee-related information for NIDA is listed below.

Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services; and Commerce, Justice, Science);
- Committee on Health, Education, Labor, and Pensions (HELP);
- Committee on the Judiciary; and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services; and Commerce, Justice, Science and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform (Subcommittee on Domestic Policy).

Many Committee and subcommittee rosters are still being finalized. To present a complete picture, details will be provided in the May 2011 Report to Council.

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International Activities

Research Results

Former Humphrey Fellows Organize Prague Declaration

Two former NIDA Hubert H. Humphrey Fellows, Pavel Bém, M.D., and Tomas Zabransky, M.D., Ph.D., organized a meeting on urban drug policy in Prague that led to the adoption of the Prague Declaration, a set of seven principles of effective drug policies and a call for greater participation of urban leaders in forming drug policies. Dr. Bém, mayor of Prague, and Dr. Zabransky, Center for Addictology, Charles University, Prague, brought together policymakers, public health administrators, and researchers for the conference, Urban Drug Policies in the Globalised World, where they discussed recent developments in the field of urban drug policy and related interventions and encouraged participants to sign the declaration.

UNAIDS Honors Palestinian Substance Abuse Research Center for Efforts To Address HIV and Drug Use

The Joint United Nations Programme on HIV/AIDS (UNAIDS) presented its prestigious Red Ribbon Award to the Substance Abuse Research Center (SARC-AMAN), Gaza. UNAIDS presents the Red Ribbon Awards at the biennial International AIDS Conference to recognize outstanding community organizations for their innovation and leadership in responding to the AIDS epidemic. The UNAIDS citation called SARC-AMAN "the first organization in Gaza to tackle issues of drug use and HIV, including stigma and misconceptions associated with these issues, in student and refugee populations." In addition to research in drug abuse and HIV/AIDS, the center also provides family counseling services; runs prevention programs for tobacco, drug use, and sexually transmitted infections; maintains a drug use monitoring system; conducts community awareness and outreach activities; and trains outreach workers, counselors, and researchers. Mohammed F. Al-Afifi, M.D., M.Sc., directs the center and has partnered with NIDA grantees and scientists in Egypt, Israel, and the United States for more than a decade on drug abuse research. Since 2003, SARC-AMAN and Dr. Al-Afifi have participated regularly in the NIDA International Forum, presenting numerous studies jointly with his research partners. Dr. Al-Afifi's research also has been supported by the World Health Organization, the United Nations Office on Drugs and Crime, the U.S. Agency for International Development Middle East Regional Cooperation Program, and STOP AIDS NOW! in The Netherlands.

NIH-Supported Meetings

Regional Meetings Foster Collaborative Research

Drug abuse and HIV/AIDS researchers across the globe are taking advantage of local meetings to bridge the regional gap that often hinders the exchange of research ideas and the development of constructive collaborations. IP-supported meetings were held recently in Vietnam, Malaysia, Norway, and Ukraine to offer

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investigators the opportunity to begin discussions and create collaboration links that could shape drug abuse research in the region. The meetings also serve to inform scientists about NIDA research funding opportunities and resources available to support new projects. Highlights of the meetings include:

- Hanoi, Vietnam. In November, 65 researchers joined NIDA and Fogarty International Center (FIC) fellowship and trainee alumni in Hanoi to initiate an Asian Regional Research Collaboration Network. Researchers from eight countries in the region (Vietnam, Thailand, Cambodia, Laos, China, Malaysia, Indonesia, and Burma) met with NIH researchers and representatives of government and international agencies to discuss regional research priorities in drug-related HIV/AIDS. The meeting was hosted by NIDA, FIC, and Hanoi Medical University, with support from the NIH Office of AIDS Research. Meeting objectives included: 1) enhancing research development in the region by networking researchers sharing common interests in prevention, treatment, and care; 2) linking current research and program implementation and evaluation from the region with programmatic activities in individual countries, such as those supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and others; and 3) providing information on current and former activities in the region for research, research training, and program implementation and evaluation. Participants were especially pleased for the opportunity to meet one another, many for the first time, and to establish a follow-up communications network using the NIDA International Virtual Collaboratory (NIVC). The NIVC group will be coordinated by a group of Asian researchers in cooperation with NIDA and FIC.
- Penang, Malaysia. Organized and led by Richard S. Schottenfeld, M.D., Yale School of Medicine, the meeting focused on the critical research needs and challenges in the region for two primary issues: epidemiology and treatment research. Participants were separated into workgroups and came away from the meeting with concrete tasks—ranging from identifying funding to the development of new research protocols—to begin to meet the substance abuse challenges in the region.
- Oslo, Norway. Held in conjunction with the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) meeting in September, co-chairs J. Michael Walsh, Ph.D., The Walsh Group, and Steven W. Gust, Ph.D., director, NIDA International Program, brought together experts in the region to discuss drugs and driving. Speakers Alain Verstraete, M.D., Ghent University, Belgium, and Dominique Lopez, European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal, discussed, in part, the challenges in gaining an accurate view of the problems with drugged driving due to differences in laws across regions and nations. The participants ended the meeting with a number of potential research projects amenable to international collaboration. During the ICADTS meeting, Flavio S. Pechansky, M.D., Ph.D., former NIDA Hubert H. Humphrey Fellow and current chair of the College on Problems of Drug Dependence International Committee, was recognized for his poster on drunk and drugged driving on Brazilian highways.
- Kiev, Ukraine. Organizers Sergey Dvoryak, M.D., Ph.D., Ukrainian Institute on Public Policy and former Hubert H. Humphrey Fellow, and David Metzger, Ph.D., University of Pennsylvania/Veterans Administration Medical Center, hosted a meeting on drug treatment and prevention among injection drug users. Invited guests, including drug abuse researchers from Armenia, Georgia, Kyrgyzstan, Russia, Tajikistan, Ukraine, and other central Asian countries, heard presentations from NIDA and other U.S. research institutions and engaged in discussions about potential collaborative studies on medically assisted treatment for drug dependence and HIV.

NIDA Supports Researchers at Hispanic Science International Conference

Sixteen NIDA-supported researchers presented their research earlier this fall in New Orleans, Louisiana, at the National Hispanic Science Network (NHSN) International Conference. This year's meeting focused on transdisciplinary

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approaches to current research agendas and the future of addiction research and treatment. The NHSN conference poster session showcased ongoing research projects to generate discussion about potential collaborations. NIDA-supported scientists from Chile, Mexico, and Spain presented their research at the International Poster Session at the conference, including:

- *Chile*: Luis Caris, University of Chile, Facultad de Medicina.
- *Mexico*: Marycarmen Bustos, Filiberto Gaytán, Alberto Jimenez, Natania Fróylan Oliva Robles, Vianney Sánchez Pineda, and Jorge Ameth Villatoro Velázquez, Instituto Nacional de Psiquiatría Ramon de la Fuente Muñiz; Octavio Campollo, University of Guadalajara; and Miguel Angel Lopez Brambila, Universidad Nacional Autónoma de México.
- *Spain*: Francisco Jesus Bueno-Cañigral, Plan Municipal de Drogodependencias; Antonio Jesus Molina-Fernandez, Proyecto Hombre Granada/University of Granada; Francisco José Montero-Bancalero, Aula de Alcoholismo.es/Instituto Bitácora; Claudia Cristina Morales-Manrique, Universidad de Valencia; Anna Robert, Hospital Benito Menni Complex assistencial en Salut Mental; Javier González-Riera, The Comprehensive Tobacco Plan for Andalusia/Jaén Health District; and Francisco Javier Romero, Instituto sobre Drogas y Conductas Adictivas.

Shedding Light on Substance Abuse in Sikkim

Drug abuse researchers gathered at a symposium in Sikkim, one of India's smallest states, to tackle some of the region's biggest health problems. Linda Cottler, Ph.D., M.P.H., a NIDA grantee, offered her expertise at the symposium in Gangtok, the capital of Sikkim, to help begin to shed light on the magnitude of substance abuse in the state. The symposium was conceived by Tekendra Rai, M.D., a NIDA Hubert H. Humphrey Fellow, who brought together Dr. Cottler, director of the Epidemiology and Prevention Research Group at the Washington University School of Medicine, and others to discuss health research methodologies and substance abuse prevention. The participants exchanged ideas on how best to obtain hard data that could help direct programs and interventions to deal effectively with the rising substance abuse and suicides among the people of Sikkim.

NIDA Supports Young International Investigators at SfN

NIDA organized an Early Career Investigators Poster Session on November 12, 2010 as part of NIDA's mini-convention on Frontiers in Addiction Research at the Society for Neuroscience Research meeting in San Diego, California. The invited poster session provides an opportunity for young investigators to speak with mini-convention symposia participants, NIDA staff, and NIDA-supported training directors and researchers while showcasing drug abuse and drug-related neuroscience research by 19 researchers from 14 countries, including:

- Yahav Dikshtein, Israel
- Chiara Giuliano, United Kingdom
- Yve Wu, Australia
- Felipe Gomez, Brazil
- Sergey Sotnikov, Russian Federation
- Joost Wiskerke, The Netherlands
- Zamberletti Erica, Italy
- Daniele Cristina de Aguiar, Brazil
- Paula Aronne, Argentina
- Maria Estela Andres, Chile
- Kaneez Fatima Shad, Pakistan
- Frank Julius Meye, The Netherlands
- Yao-Chang Chiang, Taiwan
- Engin Bojnik, Hungary

- Wojciech Solecki, Poland
- Carlo Cifani, Italy
- Ramón Sotomayor-Zárate, Chile
- Reeta Ilona Talka, Finland
- Jennifer J. Ware, United Kingdom

The international poster presenters were supported, in part, by NIDA and the College on Problems of Drug Dependence, International Brain Research Organization, International Cannabinoid Research Society, International Drug Abuse Research Society, International Narcotics Research Conference, International Union of Basic and Clinical Pharmacology Pharmacology, and Society for Research on Nicotine and Tobacco.

Online Initiatives

NIDA Staff Reviews Online Research Training Modules

NIDA staff members attended an IP briefing about free, online drug abuse research training modules available through DrugAbuseResearchTraining.org, a Web site developed by Medical Directions, Inc. (MDI), with IP SBIR funding.. The courses include biostatistics; evaluating substance abuse programs; designing and managing clinical trials; and the new neurobiology of addiction, which includes state-of-the-science interactive 3-D animation of brain pathways developed by MDI and NIDA grantee Nick Gilpin, University of California Los Angeles Laboratory of Neuroimaging. Participants at the briefing were enthusiastic about the courses and offered several suggestions about how NIDA can promote these courses among grantee, constituent, and partner organizations.

New IP Webinars Focus on Conversation and Oral Presentation Skills

As part of its online professional development series, the IP offered two, 1-hour webinars (Using Spoken English in Conversation and Scientifically Speaking: How To Prepare an Effective Talk) both designed to help drug abuse researchers prepare for scientific meetings by enhancing their skills at informal conversation and oral presentations. Participants included researchers from Australia, Bolivia, Canada, Israel, The Netherlands, Nigeria, and the United States. Both Webinars were recorded and are available for viewing any time online at: http://www.international.drugabuse.gov/collaboration/training_development.html.

Fellowships

New INVEST/CTN Fellows Selected

The IP and CTN have selected five new INVEST/Clinical Trials Network Drug Abuse Research Fellows, who will spend a year conducting mentored postdoctoral research with a NIDA grantee affiliated with one of the 16 CTN Regional Research and Training Centers. The new fellows include:

- Cecile Denis, Ph.D., University of Bordeaux, France, who will work with John Cacciola, Ph.D., and Charles O'Brien, M.D., Ph.D., University of Pennsylvania, to participate in field trials of diagnostic severity measures proposed for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The researchers will compare the DSM-5 measures with Addiction Severity Index (ASI) scores to test the: 1) feasibility of combining the two measures in the clinical evaluation of patients, and 2) sensitivity of the diagnostic-specific severity measure against the ASI measures of substance use disorder severity over time. A postdoctoral fellow in the Addiction Psychiatry Lab at the University of Bordeaux, Dr. Denis has been responsible for coordinating addiction studies, supervising clinical research associates, and training colleagues to use both the ASI and the Mini International Neuropsychiatric Interview. In addition to working on the DSM-5 field trials, Dr. Denis hopes to build on her knowledge of ASI and acquire new skills to improve assessment tools and treatment outcome measures for substance use disorders.

Sergey Dvoryak, M.D., Ph.D., Director of the Ukrainian Institute on Public Health Policy in Kiev, will use his fellowship to learn about new treatment medications and the CTN model for conducting and managing clinical trials so that he can implement national and multinational addiction treatment and HIV risk reduction studies. With his mentor, George Woody, M.D., University of Pennsylvania and CTN Delaware Valley Node, Dr. Dvoryak will finalize and submit a grant application to compare reduction in HIV injection risk behaviors and opioid use by injection drug users treated with suboxone and counseling, methadone and counseling, or counseling alone. Dr. Dvoryak was a NIDA Hubert H. Humphrey Fellow in 1999-2000, and has long collaborated with Dr. Woody and other NIDA grantees.

- Anaya Maria de L. Garcia, M.Sc., National Institute of Psychiatry, "Dr. Ramón de la Fuente Mœñiz," Mexico, will split her fellowship year between Miami and New York. In Miami, Ms. Garcia will work with Jose Szapocznik, Ph.D., University of Miami, conducting quality assurance for the Florida Node trial of the CTN Web-based delivery of psychosocial treatment protocol and helping to launch the CTN trial of hospital visits as opportunity for prevention and engagement for HIV-infected drug users. She will work with the Greater New York Regional Node under the direction of Edward V. Nunes, M.D., Columbia University and New York State Psychiatric Institute, on CTN trials in behavioral therapy; pharmacotherapy for opioid, cocaine, and cannabis dependence; Web-based delivery of psychosocial treatment; and an effectiveness trial comparing injection naltrexone plus community-based treatment with community-based treatment alone among opioid-dependent patients on parole or probation. Rushit Ismajli, M.D., Labyrinth Multidisciplinary Substance Abuse Treatment Center, Kosovo, will concentrate on learning about screening, brief intervention, and referral to treatment (SBIRT) methods during his fellowship, working with Dennis M. Donovan, Ph.D., University of Washington, and the CTN Pacific Northwest Node. A NIDA Hubert H. Humphrey Fellow in 2007-2008, Dr. Ismajli will then test an SBIRT intervention in two Kosovo secondary schools.
- Xuyi Wang, M.D., Central South University, China, will work with Walter L. Ling, M.D., University of California Los Angeles and the CTN Pacific Node, to learn about the CTN model for conducting clinical trials, analyzing data, and preparing manuscripts for publication. Dr. Wang will compare the effectiveness of contingency management with and without antidepressant pharmacotherapy versus standard medical management of methamphetamine dependence. He also will examine the effects of contingency management on general psychosocial functioning.

Secretary Clinton, NIDA Welcome New Humphrey Fellows

The NIDA Hubert H. Humphrey Fellows were among the more than 200 Humphrey Fellows from 93 countries who received a surprise visit from U.S. Secretary of State Hillary Rodham Clinton during the weeklong Humphrey Program Global Leadership Forum held each year in Washington, D.C. Secretary Clinton spoke during a reception at the U.S. Department of State, which is attended by the fellows, embassy representatives, state department officials, and representatives from partnering agencies, including Ms. Dale Weiss, program analyst from the NIDA IP, and Fellowships Administrator Ms. Lisa Jordre. Secretary Clinton welcomed the Humphrey Fellows as they began "a very worthwhile year of study," and urged the fellows to take full advantage of the opportunities the fellowship brings, "because we want you then to take what you have learned and put it to use in your own countries. You will meet friends that you never met before, both among the other Hubert H. Humphrey Fellows and here in the United States. And so you will get a chance to exchange ideas and to really test yourself." Secretary Clinton also called the Humphrey fellowships and the extensive Humphrey alumni network "an extraordinary opportunity."

Early in September, Ms. Weiss and Ms. Jordre met with the new Hubert H. Humphrey Fellows in drug abuse to introduce them to some of the NIDA resources and opportunities available to them during their fellowships. The pair met with

NIDA Hubert H. Humphrey Fellows in Substance Abuse Education, Treatment, and Prevention at Virginia Commonwealth University (VCU) and NIDA Hubert H. Humphrey Fellows in Drug Abuse and Public Health at Johns Hopkins University (JHU). Ms. Weiss described several NIDA resources, including the NIDA International Virtual Collaboratory (NIVC), a password-protected tool to support geographically distant partners in collaborative research, discussion, and education, and met individually with the fellows to discuss their professional affiliation interests.

The NIDA Hubert H. Humphrey Fellows at VCU include:

- *Dr. Rogerio Alves da Paz*, Brazil, wants to learn more about how the United States has dealt with crack epidemics, rehabilitation programs, and drug-related public policies. His fellowship goal is to establish collaborative relationships with treatment programs in the United States.
- *Dr. Dorra Amira*, Tunisia, will enhance her knowledge of drug abuse and analytical methods so that she can improve procedures in toxicology laboratories in her country. She also plans to develop greater knowledge about substance abuse prevention and treatment to better address the drug problems of Tunisia.
- *Dr. Omar El Shahawy*, Egypt, seeks to enhance his experience in drug abuse policy and prevention, with a particular focus on gender issues in adolescent and marginalized groups. He hopes to use his experience at VCU to enhance his public health competencies in fields related to substance abuse research and prevention, primarily in the area of tobacco use.
- *Dr. Ojo Abayomi Moses*, Nigeria, plans to enhance his knowledge and practical skills in the treatment and prevention of substance abuse as well as research on the common drugs of abuse in Nigeria.
- *Ms. Dafina Muqaj*, Kosovo, works as a psychologist at a drug prevention and treatment center and wants to expand her knowledge about drug treatment programs and addiction research.
- *Dr. Maia Rusakova*, Russian Federation, wants to learn new tools for the prevention of risk behavior among different target groups that could be implemented in the Russian Federation and to develop distant learning programs with the assistance of U.S. experts.
- *Dr. Mário Sérgio Sobrinho*, Brazil, plans to learn more about police procedures, judicial drug abuse cases, and the drug courts system and hopes to help the Brazilian judicial system by teaching others who are interested in improving judicial methods regarding drug abuse cases.
- *Ms. Oranooch Sungkhawanna*, Thailand, wants to design and implement more effective drug control policies and to expand the use of evidence-based substance abuse treatment and prevention programs in Thailand.

The Hubert H. Humphrey Fellows at JHU include:

- *Dr. Ayse Ender Altintoprak*, Turkey, a psychiatrist, is interested in substance abuse education and treatment.
- *Dr. Hla Aung*, Burma, a physician in family medicine, is interested in drug prevention and treatment.
- *Dr. Roman Gabrhelik*, Czech Republic, is interested in translational research, drug treatment, and epidemiology.
- *Dr. Hussein Habeeb Mhawesh*, Iraq, focuses on public health policy and management and will gain knowledge that he will use to develop policies, programs, and services toward improving health care in Iraq.
- *Dr. Rubeena Kidwai*, Pakistan, is interested in community-based programs in applied positive psychology, and developing and implementing projects to promote psychosocial wellness and psychological resilience in members of impoverished, low-income communities of Pakistan.
- *Ms. Abimbola Onigbanjo*, Nigeria, is working to improve health care and

systems for Nigerians, and has a special interest in family planning/reproductive health, maternal and child health, and HIV/AIDS.

- *Ms. Bangone Santavasy*, Laos, is interested in drugs and reproductive health, business administration, and HIV.
- *Dr. Ashish Sinha*, Nepal, is interested in drugs and HIV and will take his knowledge back to the Save the Children program in Nepal.
- *Dr. Ihor Vasiannovych*, Ukraine, wants to improve the management and evaluation of health care institutions and the accreditations of health care institutions.

USDISCA Supports Collaborations in the United Kingdom

D. Dwayne Simpson, Ph.D., emeritus director of the Institute of Behavioral Research, Texas Christian University (TCU), utilized his U.S. Distinguished International Scientist Award (USDISCA) to continue the collaborative work he began in 2005 to put in place an infrastructure for several regional initiatives and resources to target substance misuse in the United Kingdom (UK). The USDISCA supported Dr. Simpson's 3-month visit to England, Scotland, and Wales last fall to focus on structural and systemic implementation issues for clinical innovations. Ed Day, Ph.D., University of Birmingham, was the leading U.K. collaborator for the award and served as a member of the strategic planning team. During his visit, Dr. Simpson hosted a series of 30 regional seminars and group meetings with key decision makers, researchers, and opinion leaders about how to implement innovations for integrated services in substance abuse treatment and recovery. As a basis for discussion, Dr. Simpson used the TCU conceptual models for addiction treatment process and innovation implementation. His work, in part, has culminated in the creation of a center to consolidate and coordinate substance abuse prevention and recovery activities in Britain.

INVEST/CTN Fellow Targets Methamphetamine Use Among Filipino Adolescents

INVEST/Clinical Trials Network (CTN) Fellow Leonardo R. Estacio, Jr., Ph.D., M.P.H., spent his fellowship year focused on behavioral therapies to reduce methamphetamine abuse among adolescent Filipinos. Working with mentor, Dennis M. Donovan, Ph.D., at the Alcohol and Drug Abuse Institute, University of Washington, Dr. Estacio was able to hone his research skills and competencies in quantitative research and developed an appreciation for the value of the combination of both quantitative and qualitative methods in conducting research. In addition, Dr. Estacio set goals for the year to improve his grant-writing skills, share and exchange research knowledge, and develop a network for future collaborative research between U.S. and international researchers. He ended the year with clearly established plans for integrating the knowledge and skills he gained during his fellowship year, including revising the grant proposal he began with his mentor, forming a drug abuse research team to spearhead research at his university, training university and community leaders in drug abuse research and prevention, and establishing relationships with other Southeast Asian scientists for collaborations.

Dutch Summer Institute Deemed Valuable for NIDA-Supported Attendee

Ana Hilde, M.P.H., received a tuition waiver from the NIDA International Program to attend the Summer Institute on Alcohol, Drugs and Addiction in the Netherlands earlier this year. The Summer Institute, a joint initiative of ZonMw and the University of Amsterdam Graduate School of Social Sciences, is a 2-week, intensive multidisciplinary program offering graduate-level and continuing professional development training in addiction, while promoting opportunities for international networking. During the program, Ms. Hilde attended lectures, seminars, and discussions on new developments in research, policy, and practice in the field of drug addiction in the Netherlands. She heard presentations on such topics as drug policy, genetics and the neurobiology of addiction, the social context of drug use, health services research, and novel approaches to decreasing impulsivity and craving, including deep-brain stimulation with chronic heroin users. A highlight of the program for Ms. Hilde was a visit to a methadone

program where she had the opportunity to talk with patients and staff about the heroin replacement program. The Summer Institute experience has led to several new opportunities for Ms. Hilde—she has been invited to give two talks on the topic of Dutch drug programs and recently submitted an application for a NIDA research grant on adolescent initiation into prescription drug abuse.

CTN Meeting Features International Researchers

Drug abuse researchers from Brazil, Mexico, and Taiwan presented their research and sought feedback on upcoming clinical trials during the International Collaboration Workshop held at the recent NIDA Clinical Trials Network (CTN) Steering Committee Meeting. The meeting was a featured breakout session of the 3-day NIDA CTN Steering Committee Meeting. International presenters included Ronaldo Laranjeira, M.D., Federal University of Sao Paulo; Ming-Chyi Huang, M.D., Ph.D., Taipei City Psychiatric Center; and Chun-Hsin Chen, M.D., M.S., Taipei Medical University-Wang Fang Hospital. Dr. Laranjeira discussed plans to launch a clinical trial to examine the effectiveness of two promising pharmacotherapies, baclofen and modafinil, to combat crack addiction in Brazil. Walter Ling, M.D., NIDA CTN Pacific Node, talked about an upcoming trial (CTN-0048) on cocaine use reduction with buprenorphine, CURB. To date, there are no approved pharmaceutical treatments for cocaine abuse; however, buprenorphine shows promise in limited studies.

Travel Support

NIDA supported the participation of two U.S. researchers at a November 23 - 27, 2010, meeting in Mexico City on the Basic Parent Management Training-Oregon (PMTO) Model. The meeting was organized by Dr. Maria Elena Medina-Mora Icaza, Mexican National Institute of Psychiatry "Dr. Ramón de la Fuente Mœñiz," to advance the binational research project, Development and Implementation of a Training Model in Positive Parenting Practices in Mexican Families with Children Who Present Behavior Problems. The project aims to implement and evaluate the effectiveness of family-based drug abuse prevention programs in Mexico and with Latino families living in the United States. In preparation for a randomized controlled trial of the model's effectiveness, Dr. Melanie Domenech-Rodriguez, Utah State University, and Dr. Ana Baumann, Washington University, certified 12 Mexican professionals as therapists in the PMTO model to ensure the fidelity of the PMTO implementation. The collaborative research team also includes Dr. Jorge Villatoro Velázquez and Dr. Nancy Amador Buenabad of the National Institute of Psychiatry.

International Visitors

The NIDA IP hosted a group of four Iraqis taking part in the Iraq-SAMHSA Initiative. In 2008, Iraq and SAMHSA launched the Iraq-SAMHSA Initiative, in which multidisciplinary behavioral health teams from Iraq visit SAMHSA and host sites around the U.S. to learn about various interventions the teams want to adapt for implementation in Iraq. The substance abuse team visited NIDA on November 1, 2010. The visit to NIDA included a tour of the National Library of Medicine, meeting with NIDA staff including Dr. Jag Khalsa, DPMCD, Dr. Cece McNamara-Spitznas, DCNBR, Dr. Eve Reider and Dr. Tom Brady, DESPR, Dr. Petra Jacobs, CCTN and Ms. Dale Weiss, IP and visiting the Drug Court of Montgomery County, Maryland.

Four Japanese visitors from the Fujimoto Pharmaceutical Corporation visited NIDA on September 21, 2010. The focus of the visit was research on marijuana. While at NIDA the visitors met with Dr. Rao Rapaka, DBNBR and Dr. Steve Gust and Ms. Dale Weiss, International Program.

On September 23, 2010, Dr. Steve Gust and Ms. Dale Weiss, IP met with Russian Deputy Minister Veronika Skvortsova and her staff. The meeting took place under the auspices of the Bilateral Presidential Commission Health Work Group. Deputy Minister Skvortsova discussed the current substance abuse problem in Russian and Dr. Gust briefed Deputy Minister Skvortsova about recent NIDA research

findings.

Russian participants in the U.S. - Russia Bilateral Presidential Commission Drug Trafficking Working Group visited NIDA on October 20, 2010. Leading the delegation was Mr. Victor Ivanov, Director, Chairman of State Antinarcotics Committee. Meeting with the Russian delegation from NIDA were Dr. Nora Volkow, Director, Dr. Jacques Normand, ARP, Dr. Meyer Glantz, DESPR, Dr. Petra Jacobs, CCTN, Dr. Jamie Biswas, DPMDCA and Dr. Steve Gust and Ms. Dale Weiss, IP.

On November 3, 2010 a group from the Israeli Anti Drug Authority visited NIDA. The visit was organized by the U.S. Office of National Drug Control Policy. The visitors included Yair Geller, Director General, Eitan Gorni, Director Deputy and Dr. Yossi Harel-Fisch, Chief Scientist of the Israeli Anti Drug Authority. Representatives from NIDA at the meeting were Dr. Joe Frascella, DCNBR, Dr. Cindy Miner, OSPC, Dr. Petra Jacobs, CCTN, Dr. David White, DPMDCDA and Dr. Steve Gust and Ms. Dale Weiss, IP. The Israelis discussed the current prevention and treatment methods in Israel and NIDA staff briefed the Israelis on recent NIDA research findings.

As part of the U.S. Department of State World Learning Visitor Exchange Program a group of legislators, policy makers, business and civic leaders, school teachers, health care providers, academics and journalists from Mexico, Central and South America visited NIDA on November 4, 2010. The purpose of this visitor exchange program is to examine the U.S. response, both public and private, to illicit drug use, including education strategies and treatment at the national, state and local levels. While at NIDA the visitors met with Ms. Ana Anders, SPO, Dr. Ruben Baler, OSPC, Dr. Raul Mandler, CCTN and Ms. Dale Weiss, IP.

As part of a United Nations Office on Drugs and Crime study tour a group of visitors from the Russian Federal Narcological Center came to NIDA on November 30, 2010. The focus of the visit to NIDA was drug abuse and HIV/AIDS issues. NIDA staff Dr. Jacques Normand, ARP and Ms. Dale Weiss, IP and FIC staff Dr. Marya Levintova met with visitors.

Drs. Phil Skolnick, Jag Khalsa, and Ivan Montoya, all of DPMDCDA, participated in the Annual Meeting of International Society of Addiction Medicine (ISAM), in Milan, Italy, October 4-7, 2010. Phil Skolnick presented a plenary lecture at this conference.

Dr. Jag Khalsa gave a lecture at the University of Milan, October 8, 2010.

Drs. Ivan Montoya and Jag Khalsa gave lectures at the University of Padua, Italy, on October 11, 2010.

Drs. Ivan Montoya and Jag Khalsa were keynote speakers at the annual meeting of FederSerD (the Italian Society of Addiction Medicine), in Lake Garda, Italy, October 12-15, 2010.

Drs. Jag Khalsa, Dave McCann and Jane Acri of DPMDCDA presented at an invited symposium on 'Drug Abuse Morbidity and Interventions: Research at NIDA' at the Canadian Society of Addiction Medicine, in Charlotte, Prince Edward Island, Canada, October 22-25, 2010.

Drs. Wilson M. Compton, M.D., M.P.E., Elizabeth Robertson, Ph.D. and Eve Reider, Ph.D., all of DESPR, presented on "Progress in Drug Abuse and Addiction Research" to the Mentor Arabia leadership group, Washington, District of Columbia, October 14, 2010.

Dr. Wilson M. Compton, M.D., M.P.E. presented on "Mainstreaming Addictions in Medicine" at the meeting of the International Society of Addiction Medicine, Milan, Italy, October 6, 2010.

Dr. Eve Reider in the Prevention Research Branch, DESPR represented NIDA at a meeting with the Mentor Foundation that was held October 22, 2009 at the

Swedish Embassy in Washington D.C. The purpose of the meeting was for Her Majesty Queen Silvia of Sweden and Mentor to meet with and learn about the work and role of key organizations working in the drug field within the United States and explore the development of Mentor's work in the USA in order to promote positive collaboration and cooperation between organizations. Participants included members of the Mentor Foundation, Office of National Drug Control Policy, NIDA, and SAMHSA.

Dr. Eve Reider is an organizer and theme reviewer for the 3rd Annual NIDA International Poster Session that will be held June 1, 2010 at the 18th Annual Society for Prevention Research Annual Meeting, Denver, Colorado.

Eve E. Reider, Ph.D., and Wilson Compton, M.D., DESPR, met with several members of the Mentor Foundation on July 14, 2010; they included: Jeff Lee, Yvonne Thunnel, Farida Allaghi, Ph.D., Martha Givaudan, Ph.D., and Ken Winters, Ph.D. The Mentor Foundation is an international non-government not for profit organization with a focus on the prevention of drug misuse and the promotion of health and well-being of young people. Mentor seeks to identify, support and share information on effective practice that will protect young people from the harm that drugs can cause.

Dr. Peter Hartsock, DESPR, led a delegation of NIH grantees to the Clinical Microbiology and AIDS Opportunistic Infection Symposium, September 18-20, 2010 Shanghai, China. Dr. Hartsock presented on NIDA research efforts that have an impact in China, including modeling research on the expansion of hepatitis B vaccination that has encouraged the Chinese government to provide free HBV vaccinations for all children in that country. U.S.-Chinese cooperation is also increasing in the area of proteomics, just as China is poised to expand its proteomics research program.

Drs. Roy Wise and Yavin Shaham, Behavioral Neuroscience Research Branch, IRP, presented talks at the Aquitaine 2010 Conference "Insights into the Neurobiology of Addiction", October 12-15, 2010, Arcachon, France. Drs. Donna Calu and Florence Theberge also presented posters. Dr. Calu presented her research project entitled "Variations in unconditioned stimulus processing in response to changing reward value in the central nucleus of the amygdala" and Dr. Theberge presented her research entitled "Effect of heroin self-administration and subsequent withdrawal on BDNF, TrkB, and MeCP2 protein expression in the central nucleus of the amygdala".

On September 22, 2010 the following CTN INVEST fellows gave presentations.

- Dr. Meera Vaswani (India), Mentor: Dr. Wade Berrettini, University of Pennsylvania: Association of β -Arrestin Gene polymorphism in Opioid Addiction
- Dr. Suzi Nielsen (Australia), Mentor: Dr. Walter Ling, UCLA: Pharmaceutical misuse in Australia and what can be learned from the US.
- Dr. Andrea Domanico (Brazil), Mentor: Dr. Walter Ling, UCLA: Epidemiology of substance abuse in Brazil: Crack cocaine is it an epidemic now?

Dr. Felipe Vallejo (Chile) is scheduled to start his CTN INVEST fellowship on January 17, 2011. He will be working with Dr. Eugene Somoza at the University of Cincinnati.

On September 22, 2010, Drs. Petra Jacobs and Steve Gust organized an International Collaboration meeting during the NIDA CTN Steering Committee. Participants heard presentations about recent advances in substance abuse research most relevant to the CTN agenda from researchers representing Italy, Brazil, Taiwan, and the United States. Areas for common research interest included: genetics and medication development, with a special focus on the treatment of cocaine addiction.



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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Meetings/Conferences

NIDA, with contributions from NIAAA, NCI and the OBSSR, convened a conference for 140 participants: **Building Bridges - Advancing American Indian and Alaska Native Substance Abuse Research - A State of the Science and Grant Development Workshop**, October 5-7, 2010 in Rockville, MD. The goals of the conference were to review the state of the science, identify research gaps, establish next steps, facilitate networking among participants and researchers, and provide an opportunity for face-to-face technical assistance. Planning committee members from NIDA included Drs. Kathy Etz, Aria Crump, Carmen Rosa, Dionne Jones, Ms. Genna Vullo, and Mr. Ananth Charya.

NIDA's Neuroscience Consortium organized the 9th annual **Frontiers in Addiction Research Mini-convention at the 2010 Society for Neuroscience Meeting**, November 12, 2010. This year's mini-convention included sessions on the role of nicotinic receptors in the habenula in mediating addiction; Using model organisms to discover unanticipated pathways to addiction; A fresh look at dopamine release and uptake; and Connectivity of the human brain and its disruption by drugs of abuse. The mini-convention was organized by Drs. James Bjork, Jerry Frankenheim, Mary Kautz, Nancy Pilotte, Jonathan Pollock, Cathrine Sasek, John Satterlee, David Shurtleff, Roger Sorensen, David Thomas, Susan Volman, and Ms. Patricia Anderson, Usha Charya, and Joan Nolan.

Dr. Jonathan Pollock, DBNBR, chaired a symposium, **The Role of Nicotinic Receptors in the Habenula in Mediating Addiction** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in San Diego on November 12, 2010. Speakers included Drs. Okihide Hikosaka (National Eye Institute, NIH), Sarah McCallum (Albany Medical College), and Ramiro Salas (Baylor College of Medicine).

Dr. John Satterlee, DBNBR, chaired a symposium, **Using Model Organisms to Discover Unanticipated Pathways to Addiction** that was held as part of the NIDA mini-convention "Frontiers in Addiction Research" on November 12, 2010. The symposium featured presentations by Drs. Stephen C. Ekker (Mayo Clinic), Shawn Xu, Ph.D. (University of Michigan), Elissa J. Chesler (The Jackson Laboratory) and Ulrike Heberlein (University of California, San Francisco).

Drs. Jerry Frankenheim and Nancy Pilotte, DBNBR, co-chaired a symposium titled **A Fresh Look at Dopamine Release & Uptake**, at the NIDA mini-convention "Frontiers in Addiction Research" that was held November 12, 2010. Speakers included Drs. R. Mark Wightman (University of North Carolina at Chapel Hill), Susan L. Ingram (Washington State University), Stephen Rayport (Columbia University), Marisela F. Morales (NIDA), and David Sulzer (Columbia University).

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Dr. James Bjork, DCNBR, chaired a symposium on **Connectivity of the Human Brain and its Disruption by Drugs of Abuse** at the NIDA mini-convention "Frontiers in Addiction Research" held on November 12, 2010 in San Diego. Speakers at the symposium included Drs. Marcus Raichle (Washington University in St. Louis School of Medicine), Michael Greicius (Stanford University School of Medicine), F. Xavier Castellanos (New York University School of Medicine), and Elliot A. Stein (NIDA).

Dr. Susan Volman, DBNBR, again organized the **Early Career Investigators Poster Session** at the NIDA mini-convention, "Frontiers in Addiction Research" in San Diego, CA on November 12, 2010. A total of 82 posters were presented, including 7 by international investigators co-sponsored by 7 international organizations (CPDD, IBRO, ICRS, IDARS, INRC, IUPHAR and SRNT).

Drs. Mary Kautz, DCNBR and Cathrine Sasek, OSPC, chaired the 8th annual **Society for Neuroscience Jacob P. Waletsky Memorial Award lecture** at the Frontiers in Addiction Research Mini-convention at the Society for Neuroscience meeting. This year's winner was Dr. Paul Kenny. The Jacob P. Waletsky Memorial Award was established in 2003 to recognize the research contributions made by outstanding junior scientists in the area of drug addiction or alcoholism, and the nervous system.

NIDA co-sponsored with NIMH and NINDS the **4th Annual Julius Axelrod Lecture** and poster session held on November 14, 2010 at the annual Society for Neuroscience Meeting. The winner of this year's prize was Dr. Steve Heinemann from the Salk Institute. The title of his presentation was Genetic Dissection of the Role of Glutamate and Nicotinic Receptors in Synaptic Function and Disease.

Dr. John Satterlee, DBNBR, chaired a mini-symposium, **Genomic and Epigenomic Diversity of Brain DNA: What is it For?** at the annual Society for Neuroscience meeting on November 14, 2010. Speakers included Drs. Jurjen W. Westra (Genstruct Inc.), Maria Carolina (Carol) Marchetto (Salk Institute-LOGG), Courtney A. Miller (The Scripps Research Institute), Stavros Lomvardas (UCSF Mission Bay), and Skimantas Kriaucionis and Quincey LaPlant (Graduate student, Eric Nesler lab).

The NIDA Neuroscience Consortium sponsored an **NIH Grant Workshop for Early Career Investigators** at the annual Society for Neuroscience meeting, November 15, 2010. This very well attended meeting provided valuable information to those who are at the beginning of their research career. NIDA organizers included Roger Sorensen, Nancy Pilotte, Albert Avila, and Harold Gordon.

On November 1-2, 2010, the Special Populations Office (SPO), in collaboration with NIMH, NIAID, NCI, NINR, NICHD, OMH, ACF, IHS and SAMHSA, convened a research and technical assistance conference, **Health Disparities in Boys and Men: Innovative Research to Reduce Addiction, Trauma and Related Co-Morbidities**, to provide a forum to share findings and perspectives on the health disparities experienced by boys and men with a focus on drug abuse and related sequelae, identify research and program needs and opportunities, and stimulate the field to pursue research that will improve intervention programs and services.

The National CTN Steering Committee Meetings were held September 21-23, 2010 in Bethesda, Maryland. The following workshops and meetings convened:

- RUC Dissemination Workshop
- CTP and PI Caucuses
- Integrating Addiction and Healthcare Services Workshop

- CTN 0027, START
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- International Collaboration
- Invest Fellow Meeting
- Steering Committee
- Appreciation Karst Besteman
- Pharmacotherapy Special Interest Group
- CTN 0031, STAGE-12
- CTN 0049, Project HOPE

On September 21, 2010, the CTN Research Utilization Committee convened its third workshop on **Methods for Disseminating Evidence-based Treatments from the Frontlines of Community Treatment Programs.**

Approximately 70 attendees heard 5 presentations that showcased two major themes: (1) smoking cessation efforts in inpatient, residential, and outpatient programs and (2) application of the MATRIX model in intensive outpatient programs and the challenges of its dissemination, implementation, and sustainability. The specific presentations and speakers were:

- Nicotine Replacement Prescribing Trends in a Large Psychiatric Hospital before and after Implementation of a Hospital-Wide Smoking Ban. (Antoine Douaihy)
- Recovery Support Smoking Initiative (John Hamilton)
- We Still Haven't Come A Long Way Baby! Smoking Cessation Efforts in an Oregon CTP (Lucy Zammarelli and Barbara Tajima)
- MATRIX Intensive Outpatient Treatment with Adolescents (Martin Moskowitz)
- The Creation of a Dissemination Plan - the MATRIX Model (Jean Obert)

On September 24, 2010, the NIDA CCTN held a meeting entitled, **NIDA CTN Electronic Medical Records (EMR) Workshop** in Bethesda, Maryland. The meeting brought together relevant stakeholders to develop a consensus on common core data elements relevant to drug addiction treatment that could be incorporated into harmonized electronic health record systems either locally or nationwide. The purpose was to look across community treatment practices and identify common data that are obtained as a part of standard treatment and care in real-world settings.

Dr. Jonathan D. Pollock, DBNBR, organized and co-chaired the session with Dr. Lorna Role, **Habenula Session 1: Role of the Habenula in Addiction and Emotional States** at the ACNP 49th Annual Meeting held in Miami Beach, FL, December 5-9, 2010.

Dr. Vishnu Purohit organized and served as discussant, and Drs Rao Rapaka and Jack Bergman co-chaired the session, **Drug Abuse and Postpartum Depression** at the ACNP 49th Annual Meeting held in Miami Beach, FL, December 5-9, 2010.

Drs. Thomas Aigner and Susan Weiss co-organized and co-chaired a session **Drug Development- Emerging Nanotechnology- Based Drug Delivery Methods and Their Applications to Addictions Research** at the ACNP 49th Annual Meeting held in Miami Beach, FL, December 5-9, 2010.

Dr. Ruben, Baler, OSPC, co-chaired with Dr. Danny Weinberger, a session at

the ACNP annual meeting on December 8, 2010 in Miami Beach, FL titled **Neuregulin 1: A Gene at the Crossroads of Synaptic Plasticity, Psychiatric Disorders, and the Self Medication Theory of Smoking.**

Dr. Steven Grant, DCNBR, chaired a panel titled **Role of Habenula in Addiction and Depression: Worse than Expected** at the annual meeting of the American College of Neuropsychopharmacology, December 7, 2010 in Miami, Florida.

Dr. Wilson M. Compton chaired a panel on **Intersecting Neurobiology and Epidemiology and Neuroscience of ADHD and Drug Addiction** at the American College of Neuropsychopharmacology, Miami, Florida, December 8, 2010.

Dr. Kevin Conway presented a poster entitled **Severity of Addiction: The Need for a New Instrument** at the American College of Neuropsychopharmacology in Hollywood, Florida, on December 7, 2010.

Dr. Cindy Miner, Deputy Director, OSPC presented at "The Impact of Research on Policy and Practice: Recent Successes, Discussions and Future Directions of the NIDA/SAMHSA Blending Initiative" on August 23, 2010 in Baltimore, MD.

Dr. Cindy Miner participated in a plenary session at the National Prevention Network Prevention Research Conference on September 3, 2010 in Denver, Colorado.

Dr. Cindy Miner delivered the keynote "The Promise of Science: Blending Research and Practice" at the National Conference on Addiction Disorders (NCAD) on September 8, 2010 in Washington, DC.

On October 14, 2010, Dr. Ruben Baler, OSPC, lectured on the Neuroscience of Addiction to freshman students in the "Understanding Drug Abuse" Course at the Georgetown University School of Public Health, Mount Vernon Campus.

Dr. Lula Beatty co-chairs the Data, Research and Evaluation Committee of the Federal Interagency Health Equity Team (FIHET). Members of the committee include staff from NIMH, NINR, CDC, NIMHD, and NIDRR. The FIHET is coordinated through the DHHS Office of Minority Health and was established to provide guidance in the implementation of the research objectives of the National Partnership for Action to End Health Disparities, the national health disparities plan developed by OMH.

Dr. Lula Beatty participated as a faculty mentor at the HATT Institute on November 15 -16, 2010 at the University of California, Los Angeles. The UCLA HIV/AIDS Translational Training Program is a collaboration of the Center for Culture, Trauma and Mental Health Disparities (CCTMHD), the UCLA AIDS Institute and the Center for HIV Identification, Prevention and Treatment Services (CHIPTS). HATT provides multi-disciplinary, state-of-the-art training to better equip postdoctoral fellows and early career investigators to submit and receive NIH grant funding.

Dr. Lula Beatty attended the Annual Legislative Conference sponsored by the Congressional Black Caucus Foundation, September, 2010 in Washington, DC. Ana Anders, M.S.W., Public Health Analyst, SPO, attended "Advancing Latino Behavioral Health: From Margin to Mainstream," the Latino Behavioral Health Institute's annual conference as a representative of NIDA on September 22-24, 2010 in Los Angeles, CA.

Ana Anders attended "Modeling a Transdisciplinary Approach to Current Research Agendas," the National Hispanic Science Network on Drug Abuse's (NHSN) annual conference, September 31- October 2, 2010 in New Orleans, LA.

On November 8, 2010, Pamela Goodlow of NIDA's Special Populations Office met with students and faculty at Howard University in Washington, DC, at an NIH-sponsored forum. She discussed NIDA and NIH research opportunities available to students at all levels throughout the school year and during the summer.

Dr. Phil Skolnick, Director, DPMCD, lectured at the Collaborative Drug Discovery Conference, UCSF, October 21, 2010.

Dr. Phil Skolnick chaired a session at the American College of Neuropsychopharmacology Meeting, December 5-9, 2010.

Dr. Jag Khalsa, DPMCD, moderated a session on Social and Psychiatric Issues in HIV at the 'HIV and Liver Disease' meeting, Jackson Hole, Wyoming, September 22, 2010.

Drs. Jag Khalsa, Dave McCann and Jane Acri of DPMCD presented at an invited symposium on 'Drug Abuse Morbidity and Interventions: Research at NIDA' at the Canadian Society of Addiction Medicine, in Charlotte, Prince Edward Island, Canada, October 22-25, 2010.

Dr. Jag Khalsa moderated a session on Community Treatment centers in America at the National Conference on Treatment Communities, in Washington, November 8-9, 2010, where Dr. Bob DuPont, former NIDA Director, Dr. Don Kurth of ASAM, and Dr. Greg Bunt of DayTop and ASAM, presented the current status on integrated treatment successes in treatment communities in the US.

Dr. Jag Khalsa moderated a session on Social and Psychiatric Issues in HIV at the 'HIV and Liver Disease' meeting, Jackson Hole, Wyoming, September 22, 2010.

Dr. Vishnudutt Purohit and Dr. David Thomas organized a symposium on **Sex Differences in Pain and Opioid Analgesia** held in Rockville, Maryland on October 13, 2010. The symposium covered four topics: 1) Sex and Gender Differences in Pain: An Overview by Dr. Roger B. Fillingim, University of Florida; 2) Sex Differences in Sensitivity to Opioid Analgesia: Role of Gonadal Hormones by Dr. Rebecca M. Craft, Washington State University; 3) Role of Periaqueductal Gray in Sexually Dimorphic Actions of Morphine by Dr. Anne Z. Murphy, Georgia State University; and 4) Sex-dependent Function of Spinal Mu and Kappa Opioid Systems by Dr. Alan Gintzler, State University of New York Downstate Medical Center. The symposium was inaugurated by Dr. David Shurtleff; introduced by Dr. Vishnudutt Purohit; chaired by Dr. David Thomas and Dr. Cathrine Sasek; and discussed by Dr. Rao Rapaka and Dr. Cora Lee Wetherington.

Dr. Cora Lee Wetherington, Coordinator, Women and Sex/Gender Differences Research and DBNBR, represented NIDA at the NIH Office of Research on Women's Health (ORWH) 20th anniversary event in Natcher Auditorium, September 27, 2010, and at the ORWH Congressional briefing presentation of the 2020 NIH Strategic Plan for Women's Health Research, September 30, 2010.

Dr. Cora Lee Wetherington was a session moderator in the conference, "Enrolling Pregnant Women: Issues in Clinical Research," held by the NIH Office of Research on Women's Health (ORWH), October 18, 2010 in Bethesda, MD. NIDA-grantees, Hendree Jones and Kim Yonkers were speakers in the conference.

Dr. Cora Lee Wetherington participated in the annual meeting of the Directors of the ORWH Building Interdisciplinary Research in Women's Health (BIRCWH) Program, November 8, 2010, Bethesda, MD. She also participated in the annual Directors meeting for the ORWH Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health Program,

November 8, 2010, Bethesda, MD. The BIRCWH program is an interdisciplinary career development program consisting of K12 grants and the SCOR program consists of P50 center grants.

Dr. Cora Lee Wetherington was a session moderator in the 7th annual Interdisciplinary Women's Health Research Symposium sponsored by the NIH Office of Research on Women's Health, November 9, 2010, Masur Auditorium, NIH Campus, Bethesda, MD. NIDA-supported presenters included Kevin M. Gray (Medical University of South Carolina) and Marc N. Potenza (Yale University School of Medicine.)

Dr. Cora Lee Wetherington co-organized and co-chaired with Dr. Shelly F. Greenfield, Harvard Medical School, the symposium, "Sex/Gender Differences and Women-Specific Issues in Drug Abuse," at the annual meeting of the American Academy of Addiction Psychiatry, Boca Raton, FL, December 2-5, 2010. The speakers were Kathleen T. Brady (Medical University of South Carolina), Rajita Sinha (Yale University School of Medicine), Shelly F. Greenfield (Harvard Medical School), Denise A. Hien (Columbia University), and Frankie Kropp (University of Cincinnati College of Medicine).

Dr. Samia Noursi, DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research, participated in the Executive Committee meeting of the National Partnership to End Interpersonal Violence (NPEIV), September 10, 2010, San Diego, CA.

Dr. Samia Noursi participated in the annual Think Tank Meeting of the National Partnership to End Interpersonal Violence (NPEIV), September 11, 2010, San Diego, CA.

Dr. Samia Noursi chaired a keynote panel entitled "Providing Gender-Specific Trauma-Informed Substance Abuse Treatment" at the 15th International Conference on Violence Abuse & Trauma, September 12-15, 2010, San Diego, CA.

Dr. Samia Noursi and Dr. Dionne Jones, DESPR chaired an invited panel entitled "Adolescent Substance Abuse & Its Consequences" at the 15th International Conference on Violence Abuse & Trauma, September 12-15, 2010, San Diego, CA. Dr. Wendee Wechsberg (RTI International) presented on "The Allure of Gangs, Violence and Victimization Experienced by Drug-using Teens in Cape Town, South Africa" and Dr. Jamila Stockman (University of California Los Angeles) presented on "Continuums of Sexual Coercion among Adolescents: Pathways to Substance Abuse".

Dr. David Shurtleff, Director, DBNBR, gave the keynote address "An Update on Drug Abuse and Addiction Research" at the F. Ivy Carroll Symposium: 50 Years of Research at RTI, held at the Sheraton Imperial Hotel & Convention Center in Durham, NC. November 1, 2010.

Dr. John Satterlee, DBNBR, gave a presentation entitled The Roadmap Epigenomics Program at an NICHD- sponsored meeting on Epigenetics and Intellectual Disabilities, North Bethesda, MD, Sept 27-28, 2010.

Dr. Da-Yu Wu and Dr. Jonathan D. Pollock organized and chaired the web-based conference, "Molecular Basis of Adolescent Brain Development and How These Mechanisms Are Influenced by Abused Drugs", December 16, 2010. This webinar was attended by many of the most prominent researchers in the areas of basic brain development, adolescence and addiction. The panel members assessed the current progress in the field, identified bottlenecks and possible breakthroughs, and provided vision and leadership recommendations to NIH for fostering the best research for adolescent studies relevant to substance abuse and addiction.

Drs. Laurence Stanford and Joseph Frascella, DCNBR, participated in NIDA's

Drug Facts Chat Day on November 8, 2010.

Dr. Laurence Stanford participated in NIDA activities at the USA Science and Engineering Festival Expo held October 23 and 24, 2010 on the National Mall in Washington DC.

Dr. Joseph Frascella attended the annual meeting of the National Hispanic Science Network entitled: "Modeling a Transdisciplinary Approach to Current Research Agendas" held September 30 - October 2, 2010 in New Orleans, LA.

Dr. Cheryl Anne Boyce, DCNBR, presented at the NIDA co-funded annual meeting of the Translational Research Consortium on Child Neglect, September 23-24, 2010 in St. Louis, MO.

Dr. Nicolette Borek, DCNBR, presented a talk on Prenatal Nicotine Exposure and Development at the Fall Network meeting of the Pediatric HIV/AIDS Cohort Study (PHACS) in Baltimore Maryland, September 30-October 1, 2010.

Dr. Nicolette Borek participated in the Concept Paper Analysis Session at the Building Bridges: Advancing American Indian/Alaska Native Substance Abuse Research - A State of the Science and Grant Development Workshop, October 5-7, 2010 in Rockville, MD.

Dr. Cheryl Anne Boyce presented on Grant Writing, and Dr. Nicolette Borek presented on Child and Adolescent Research Opportunities at NIDA during a workshop at the 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 26-28, 2010. Dr. Boyce also chaired a symposium on child maltreatment and drug abuse at the meeting.

Dr. Karen Sirocco, DCNBR, participated as NIDA representative for the preconference experts' roundtable on early development and meeting of the 10th anniversary of the Institute of Medicine-National Research Council publication of From Neurons to Neighborhoods on October 27-28, 2010 in Washington, DC.

Dr. Nicolette Borek represented NIDA at the meeting Behavioral Epigenetics held in Boston, MA, October 29-30, 2010. The meeting was organized by Drs. Barry Lester, Edward Tronick and Eric Nestler and co-sponsored by The New York Academy of Sciences, Brown University, the University of Massachusetts, NIDA, NICHD, NIMH, and OBSSR.

Dr. Yu (Woody) Lin served as a member of a steering committee of the NIH Pain Consortium Workshop entitled, "Pharmacological Management of Chronic Pain in Older Adults" held at NIH on September 14-15, 2010. He moderated a session at the workshop entitled "Role of Current Databases in Research on Pharmacological Management of Chronic Pain in Older Persons with Particular Attention to Opioids and NSAIDs."

Dr. Yu (Woody) Lin of DCNBR, together with Dr. David Thomas of DNBDR and Dr. Richard Denisco of DESPR, organized a NIDA workshop on Medical/Dental/Nursing Students Pain Education held in Bethesda, MD. on September 24, 2010.

Dr. Yu (Woody) Lin participated in the initial meeting on FDA's Safe Use Initiative-Collaborating to Reduce Preventable Harm from Medications held in Bethesda, MD on July 27, 2010.

Dr. Yu (Woody) Lin was invited to, and participated in, an FDA Round Table Discussion on Safe Use of Pain Management and the Elderly in Bethesda, MD on September 30, 2010.

Dr. James Bjork, together with Dr. Lis Nielsen of the National Institute of Aging, coordinated a session entitled "Federal Funding Opportunities for Neuroeconomics-A Roundtable Discussion with NIH and NSF Program Officials."

at the Society for Neuroeconomics Annual Conference, held on October 16th, 2010 in Evanston, IL.

Dr. James Bjork attended the all-hands kick-off conference for the Human Connectome Project (HCP) on September 28-29, 2010 in St. Louis, MO. Dr. Bjork was appointed to the task-related neuroimaging Operations Team and the neurocognition Operations Team of the HCP. The HCP is an NIH Neuroscience Blueprint initiative to obtain a "gold-standard" dataset of the connectivity of the healthy adult brain.

Drs. Shoshana Kahana and Will Aklin, DCNBR, served as a moderator and discussant for several sessions at the Seek, Test, and Treat in Criminal Justice Settings meeting in Bethesda, MD from November 15-16, 2010. The meeting was sponsored by the AIDS Research Program at NIDA and was organized by Redonna Chandler of DESPR.

Dr. Shoshana Kahana was invited to join colleagues from the CDC, NIMH, and other external stakeholders to participate in generating final guidelines on "Efficacy Criteria for Evaluating Individual- and Group-level HIV Medication Adherence Interventions Conducted in the U.S." These Guidelines are expected to be released by the CDC in December 2010.

Dr. Cecelia Spitznas, DCNBR, was a discussant for a symposium at the Association for Cognitive and Behavioral Therapy in San Francisco, CA on November 18, 2010. The symposium's purpose theme, how mobile assessment and treatments are changing conceptualization and treatment of addiction and psychopathology, served to stimulate interest in how research on wireless approaches help reconceptualize psychopathology and offer potential to address high rates of relapse for patients in traditional counseling by providing on demand treatment options. NIDA grantees participating included Dr. Linda Dimeff, Edward Boyer and Lisa Marsch.

Drs. Will Aklin, Geetha Subramaniam, and Lisa Onken, of the Behavioral & Integrative Treatment Branch, DCNBR, in collaboration with DESPR, organized and served as collaborators and discussants on a meeting on Screening & Brief Intervention & Referral to Treatment. The meeting of SBIRT grantees was held in Bethesda on September 30-October 1, 2010.

Dr. Lisa Onken gave a presentation entitled "The Stage Model of Intervention Development: A Bidirectional + Translational Conceptual Framework" and led a Breakout Session at the NHLBI/OBSSR sponsored workshop Translating Ideas into Interventions: The Process of Developing Behavioral Interventions on December 6-7, 2010, in Washington, DC. This workshop included investigators from the NHLBI ORBIT (Obesity-Related Behavioral Intervention Trials) group, as well as other researchers involved in research on behavior change interventions.

Dr. Wilson M. Compton, Director, DESPR, continues to participate in the White House Office of National Drug Control Policy Interagency Workgroup on a continuing basis.

Dr. Wilson M. Compton continues to participate in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings on a continuing basis.

Dr. Wilson M. Compton presented on "Intersecting Epidemiology and Neuroscience of Stress and Addiction" at New York University New Frontiers in Research and Practice symposium, New York, New York, December 10, 2010.

Dr. Wilson M. Compton presented a plenary lecture on "Progress in Addictions Research" at the annual meeting of the National Center for Responsible Gaming, Las Vegas, Nevada, Sunday, November 14, 2010.

Drs. Wilson M. Compton and Peter Hartsock, DESPR, co-chaired a panel on

"Social Epidemiology Applied to Understanding Disparities Among Injecting Drug Users (IDUs)" at the American Public Health Association annual meeting, Denver, Colorado, November 8, 2010.

Dr. Wilson M. Compton presented a plenary lecture on "Future Directions for Research on Recovery and Relapse" at the Institute for Behavioral Health McGovern Award symposium, Washington, District of Columbia, November 4, 2010.

Dr. Wilson M. Compton presented a plenary lecture on "Progress on Drug Abuse and Addiction Research" at the Health Disparities in Boys and Men: Innovative Research to Reduce Addiction, Trauma and Related Co-morbidities symposium, Washington, District of Columbia, November 1, 2010.

Dr. Wilson M. Compton presented plenary lectures on "Mainstreaming Addictions in Medicine" at the meetings of the American Association for the Treatment of Opioid Dependence, Chicago, Illinois, October 27, 2010 and the Addiction Health Services Research Conference, Lexington, Kentucky, October 26, 2010.

Dr. Wilson M. Compton presented a plenary lecture on "Trends in Drug Abuse: Implications for Family Interventions" for the White House Office of National Drug Control Policy Rebecca Project symposium, Washington, District of Columbia, September 28, 2010.

Dr. Wilson M. Compton presented to the American Psychiatric Association's Expert Advisory Panel on Addiction Psychiatry, Arlington, Virginia, September 23, 2010.

Dr. Eve Reider, DESPR, was invited to attend and represented NIDA on July 20, 2010 at the 1st In-Progress Review (IPR) of extramural research on Substance Abuse and Psychological Resilience of the Military Operational Medicine Research Program (MOMRP). The meeting was conducted by Carl A. Castro, Ph.D., Colonel, U.S. Army, Director, and MOMRP and was held in Frederick, MD.

Drs. Kevin Conway and Bennett Fletcher, DESPR, organized a symposium entitled "Criminal Justice Research Funding at the National Institute on Drug Abuse" for the American Society of Criminology in San Francisco, California, on November 17, 2010.

Dr. Meyer Glantz, DESPR, participated in the American Psychological Association's sixth annual Science Leadership Conference (SciLC). The conference was held in Washington, DC, on November 12-13, 2010. The theme of the 2010 SciLC was Strengthening Our Science: Enhancing the Status of Psychology as a STEM Discipline.

Dr. Eve Reider represented NIDA and participated in the Center for Substance Abuse Prevention's Native American Center for Excellence Substance Abuse Prevention meeting "Indigenous Research and Evaluation Summit 2010: Bridging Indigenous Roots to Contemporary Lives." The meeting was held September 1 and 2, 2010 at the Ala Moana Hotel in Honolulu, Hawaii.

Dr. Eve Reider is representing NIDA on a recently developed HHS Adolescent Health Working Group and attended her first meeting on September 7, 2010 at the Hubert Humphrey Building.

Dr. Reider is involved in a sub-committee that is focused on Preventing and Addressing Mental Disorders and Promoting Mental Wellness Among Adolescents.

Richard Denisco, M.D., M.P.H., DESPR, is serving on the Clinical and Rehabilitative Medicine Research Program, US Army Medical Research and

Materiel Command, Acute and Chronic Pain Advisory Committee. Dr. Denisco gave a presentation on the NIH Pain Program and the PROMIS Program at the last meeting September 15, 2010.

Richard Denisco, M.D., M.P.H., co-organized and co-chaired a meeting on "Medical Education on Pain Medicine for Medical/Dental/Nursing Students," September 24, 2010 at the NSC in Bethesda, MD. This meeting was co-sponsored by NIDA Prescription Opioid and Pain (POP) Workgroup and the NIH Pain Consortium.

Richard Denisco, M.D., M.P.H., co-organized and co-chaired a meeting sponsored by DESPR and DCNBR, on "Screening, Brief Intervention and Referral to Treatment" September 30, 2010 and October 1, 2010 the NSC in Bethesda, MD. Fifteen PIs' and a number of world respected leaders in SBIRT attended.

Dr. Peter Hartsock, DESPR, participated in a research symposium and site visits at the University of Texas School of Public Health, September 17-18, 2009, Houston, TX. Dr. Hartsock presented on NIDA's HIV/AIDS research program, including research in advanced mathematical modeling and applied epidemiology.

Dr. Peter Hartsock met with the Virginia Commonwealth University (VCU) Humphrey Fellows specializing in drug abuse to discuss NIDA's research program, the interests Fellows have for conducting research in their respective countries, and applying for NIDA grants, October 13, 2010, Richmond, VA.

Dr. Peter Hartsock presented on NIDA's mission to the new Humphrey Fellows at Virginia Commonwealth University on November 17, 2010, in Richmond, VA. Other topics included research and training opportunities and how to contact NIDA program staff about potential future grant applications.

Drs. Naimah Weinberg, DESPR, and Geetha Subramanian, DCNBR, submitted, and Dr. Weinberg chaired, a symposium on "Adolescent Substance Abuse and Internalizing Disorders: Moving Beyond the Myths" at the annual meeting of the American Academy of Child & Adolescent Psychiatry, in New York City, October 25-29, 2010.

Dr. Aria Crump, DESPR, organized a session for the U.S. Department of Education 2010 National Meeting on Alcohol and Other Drug Abuse and Violence Prevention in Higher Education. The session, entitled "Preventing Drug Abuse in Institutes of Higher Education: Research Based Approaches to Understanding and Responding to the Problem," took place on October 19, 2010 at the Gaylord National Conference Center in Maryland.

Dr. Richard A. Jenkins participated in the OAR Social and Behavioral HIV Prevention Research Think Tank that was held on September 26-28, 2010 in Bethesda, MD. This meeting was focused on development of new strategies for HIV prevention research.

Dr. Petra Jacobs, CCTN, chaired a session entitled "HIV Testing, Counseling, and Treatment in OTPs - New Research Findings and Clinical Implications" at the 2010 AATOD National Conference held in Chicago, IL, October 23-27, 2010.

Drs. Geetha Subramaniam and David Liu, CCTN, organized and chaired a symposium titled "Beyond Main Findings of NIDA Multi-Site Treatment Trials for Youth with Substance Use Disorders: What Works and for Whom?" at the 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, held October 26-31, 2010, in New York, New York.

The Addictions 2010 conference was held October 28-31, 2010 in Arlington, Virginia. On October 31, Dr Harold Perl, CCTN, gave an invited address, titled "Addicted to Discovery: Does Our Quest for New Knowledge Hinder Practice

Improvement?" at the conference titled "The New Frontier in Addiction Treatment: Evidence-Based Policy and Practice."

Dr. Mary Ellen Michel, CCTN, moderated a session entitled "15th Anniversary of Alcohol, Tobacco & Other Drugs Section and 10th Anniversary of the Clinical Trials Network: Progress Together" at the 138th annual meeting of the American Public Health Association held in Denver, CO November 6-10, 2010.

Dr. Udi Ghitza, CCTN, chaired a workshop entitled "Electronic Health Records (EHR) and Addiction Medicine Care Delivery: NIDA's effort in facilitating the development and implementation of EHR" at the 21st annual meeting of the American Academy of Addiction Psychiatry (AAAP) held in Boca Raton, FL, December, 2-5, 2010.

Dr. Mark Swieter, OEA, was appointed Chair of the Writing Resumes and Summaries of Discussion Working Group with representatives from 9 ICs and CSR. He presented workgroup recommendations to the NIH Review Policy Committee on November 17, 2010 and the report and recommendations to the NIH Extramural Program Management Committee on January 6, 2011.

Dr. Meena Hiremath, OEA, was a panelist in the discussion about "Review considerations, key elements, and grantsmanship at the "Building Bridges: Advancing American Indian/Alaska Native Substance Abuse Research--A State of the Science and Grant Development Workshop" in Rockville, Maryland on October 5-7, 2010.

Dr. Meena Hiremath, OEA, was a NIDA Staff participant in the roundtable meetings with individuals seeking technical assistance at the "Building Bridges: Advancing American Indian/Alaska Native Substance Abuse Research--A State of the Science and Grant Development Workshop" in Rockville, Maryland on October 5-7, 2010.

Dr. Nadine Rogers, OEA, served as a group facilitator during a book discussion with the author of "The Immortal Life of Henrietta Lacks (HeLa)" while attended the Advancing Ethical Research Conference, organized by PRIM&R, in San Diego, CA from December 6 - 8, 2010.

On November 15, 2010, Dr. Teri Levitin, OEA, participated in a focus group sponsored by the NIH Office of Human Resources to obtain ideas relevant to establishing an NIH-wide leadership development program for high potential employees in GS 12-14 positions and Title 42 equivalents.

On November 22, 2010, Dr. Levitin, OEA, participated in an NIH sponsored focus group to obtain perceptions about research management and portfolio analysis.

Brian H. O'Laughlin, OM, served on the planning committee and presented on Vendor Pay Issues at the 2010 NIH Acquisition Symposium titled "The Bugs are Getting Meaner- NIH: Protecting the Nation's Health" held on November 1-3, 2010 in Cambridge, Maryland.

Dr. Amy Newman, IRP, gave invited lectures at the University of Texas Health Science Center, Department of Pharmacology, San Antonio, Texas and the University of Maryland, Department of Chemistry, College Park, Maryland, both in September 2010.

Dr. Toni Shippenberg, Chief, Integrative Neuroscience Branch, IRP, chaired a nanosymposium at the annual Society for Neuroscience meeting in November 2010.

Dr. Qing-Rong Liu, Neurobiology of Relapse Section, IRP, presented at the Behavioral Epigenetics Conference, October 29-30, 2010, Boston, MA. The title of his abstract was "Effect of Heroin Self-Administration and Subsequent

Withdraw on Central Amygdala and Hippocampus BNDF and MECP2."

Dr. Liu presented an abstract at The American Society of Human Genetics Meeting, November 2-6, 2010.

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Media and Education Activities

National Drug Facts Week

On November 8th, 2010, NIDA launched its first annual National Drug Facts Week (NDFW), a health observance for teens aimed to shatter the myths about drugs and drug abuse. During the week, NIDA encouraged teens to get factual answers from scientific experts about drugs and drug abuse through community-based events around the country, activities on the Web, TV news stories and other outreach measures. Efforts yielded over 90 community-based events in more than 20 states nationwide, with scientists talking to groups of teens as large as 1,000. NIDA also launched its first annual "National Drug IQ Challenge," a 20-question multiple choice quiz that teens and adults can take to test their science-based knowledge about drugs. The quiz was taken by more than 12,000 users alone on the NIDA Web site, and many more at community events. NIDA also launched the new Teen Substance Abuse Awareness through Music Contest, a collaboration with MusiCares[™] and the GRAMMY Foundation[™], the two non-profit organizations associated with the Recording Academy. Teen winners received a backstage pass to an upcoming GRAMMY rehearsal. NIDA's media activity for National Drug Facts Week, including a Satellite Media Tour with Dr. Nora Volkow in 21 media markets, reached more than 20 million people. In addition, other NIDA scientists conducted a webinar and Facebook chat via *Discovery Education*.

<http://drugfactsweek.drugabuse.gov/index.php>

Additional National Drug Facts Week Activities

Discovery Education Channel Webinar: Drs. Susan Weiss and Gaya Dowling from NIDA, along with Dr. Amy Eichner from the US Anti-Doping Agency (USADA) presented a webinar called "Shatter the Myths" geared towards middle/high school teachers and their students, which focused on marijuana, prescription drug abuse, and performance enhancing drugs. This took place on November 3, 2010, and feedback from the ongoing chat was extremely positive. The webinar's reach was estimated at 1000 participants. It has been archived and can be viewed at:

<http://blog.discoveryeducation.com/blog/2010/11/08/shatter-the-myths-webinar-archive/> Dr. Susan Weiss also spoke to approximately 300 students at TC Williams High School in Alexandria, Virginia on November 10th, 2010. Her goal was to "shatter the myths"—particularly concerning marijuana and prescription drug abuse.

Chat Day

On November 9, 2010, NIDA held its fourth annual Drug Facts Chat Day from 8 am to 6 pm EST, as part of National Drug Facts Week. The NIDA Chat Day team—more than 40 people strong—answered almost 1,600 questions, up from 1,200 questions in 2008 and 2009. This year, the four most commonly asked about topics were marijuana, alcohol, nicotine and prescription drugs. Interestingly, there were many more questions about prescription drugs this

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year—indicating that teens are finally beginning to connect non-medical use of prescription drugs with drug abuse. Chat Day also had representatives from NIAAA and NIMH participate for the first time. The Chat Day transcript is posted at <http://www.drugabuse.gov/chat/>.

NIDA participated in the first national science festival to be held in the United States, the **USA Science & Engineering Festival**, October 23-24, 2010. The festival, which was held on National Mall and Freedom Plaza, was designed to generate interest among our nation's youth as well as adults in science, technology, engineering, and math. NIDA's exhibit featured "NIDA Brain Derby", an interactive game designed for children; videos designed for high school children; and human brain demonstrations. The festival, including NIDA's exhibit, was very successful, with the number of people who attended far exceeding anyone's expectations. NIDA staff—from both the intramural and extramural programs—and including the Director, were key to the success of this event.

SfN Conference

NIDA Director Dr. Nora Volkow and other NIDA staff presented and/or attended the *Frontiers in Addiction Research: NIDA Mini Convention at the Society for Neuroscience 40th Annual Meeting*, San Diego, CA, on November 8-14, 2010. To highlight the research presented at the mini-convention, two NIDA scientists, Drs. Gaya Dowling and David Thomas, tweeted throughout the meeting. Results of their efforts included a total cumulative reach of over 90,000 followers, 52 retweets and 18 mentions, as well as 76 new followers. The NIDA Press Team also developed a Special Neuroscience Issue of *NIDA NewsScan* highlighting the research presented at the convention, which can be seen at <http://www.nida.nih.gov/PDF/newsscan/newsscan69.pdf>.

Centers of Excellence

To improve drug abuse and addiction training of future physicians, through NIDAMED's Centers of Excellence for Physician Information Program, three new curriculum resources were launched in November, at the Association of American Medical Colleges 2010 Annual Meeting's *Innovations in Medical Education* in Washington, DC.

Included were:

- an objective structured clinical exam (OSCE) from Boston University School of Medicine on opioid risk management, which covers how to initiate and manage long-term opioid pain therapy in patients with chronic pain, and how to discuss risks and benefits of opioids for chronic pain with patients
- a lecture presentation from the University of North Dakota School of Medicine & Health Sciences on how to talk to patients about sensitive subjects, including drug/alcohol use and abuse, intimate partner violence, and sexual history/concerns
- a methamphetamine lecture and interclerkship, developed by Creighton University, that introduces learners to methamphetamine abuse and dependence, including methods of abuse, methamphetamine's stimulant effects, and the short- and long-term effects on users

Monitoring the Future Press Conference

On December 14, 2010, NIDA hosted a press conference announcing the results of the annual Monitoring the Future survey. Panelists included NIDA Director Nora D. Volkow, ONDCP Director Gil Kerlikowske, and the survey's principal investigator, Dr. Lloyd Johnston. The press conference highlighted the publication of the Monitoring the Future Survey results, which can be found at <http://www.drugabuse.gov/drugpages/MTF.html>. Since 1975, the MTF survey has measured drug, alcohol, and cigarette use and related attitudes among adolescent students nationwide. Survey participants report their drug use behaviors across three time periods: lifetime, past year, and past month. The

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survey is funded by NIDA and conducted by the University of Michigan.

Press Releases, Media Advisories & Notes to Reporters

Press Releases & Media Advisories

September 10, 2010 — A press release titled "**NIH, MusiCares and the GRAMMY Foundation Announce Teen Music Contest**" was distributed announcing NIDA's Teen Substance Abuse Awareness Music Contest to coincide with National Drug Facts Week.

September 13, 2010 — A press release titled "**Latent HIV Infection Focus of NIDA's 2010 Avant-Garde Award**" was distributed announcing that Dr. Eric M. Verdin of the J. David Gladstone Institutes in San Francisco, CA, was selected as the 2010 recipient of the NIDA Avant-Garde Award for HIV/AIDS Research for his proposal to study the mechanisms of latent HIV infection.

September 21, 2010 — A press release titled "**First NIDA Avant-Garde Awards for Medications Development Research**" was distributed announcing the recipients of the first-ever Avant-Garde Awards for Innovative Medication Development Research.

September 23, 2010 — A press release titled "**Unprecedented Effort to Seek, Test, and Treat Inmates with HIV**" was distributed announcing twelve scientific teams in more than a dozen states that will receive NIH grants to study effective ways to prevent and treat HIV/AIDS among people in the criminal justice system.

November 10, 2010 — A press release was issued to unveil the winners of the MusiCares and GRAMMY Foundation's Teen Substance Abuse Awareness through Music Contest.

Other Press Releases

November 5, 2010. President Honors Outstanding Early-Career Scientists. President Barack Obama named Mauricio R. Delgado, Ph.D. (Rutgers University), a NIDA-funded grantee, as one of the 85 researchers who are recipients of the Presidential Early Career Awards for Scientists and Engineers, the highest honor bestowed by the United States government on science and engineering professionals in the early stages of their independent research careers.

November 19, 2010. A Statement from the NIH Director, Francis S. Collins, M.D., Ph.D., on the Presidential Early Career Award for Scientists and Engineers (PECASE) recipients. Mauricio R. Delgado, Ph.D. of Rutgers University, a NIDA-funded grantee, was announced as one of the eighteen NIH grantees and two intramural scientists who have been selected by the White House Office of Science and Technology Policy to be among this year's 85 researchers to receive this presidential award, the nation's highest honor for scientists at the beginning of their professional careers.

Notes to Reporters

October 6, 2010 — A note to reporters was issued about a NIDA-funded study published in *Addiction* that compared two treatments for neonatal abstinence syndrome (NAS), a condition affecting infants exposed to opiates before birth.

October 8, 2010 — NIDA issued a note to reporters about the latest message from Dr. Volkow on the website announcing NIDA's support of the "Functional Connectomes Project."

October 13, 2010 — Reporters were informed through a note to reporters about two breaking developments which represent dramatic advances in treatment for people addicted to heroin and prescription opioid painkillers.

October 15, 2010 — A note to reporters was issued about a new NIDA-funded research paper about cocaine published online in Science.

October 27, 2010 — Reporters were sent a note to highlight a new NIDA-funded research paper published in the Journal of the American Academy of Child & Adolescent Psychiatry about results of a Lifetime Prevalence of Mental Disorders in U.S. Adolescents.

Research News

Full NewsScans can be seen at

<http://www.nida.nih.gov/NIDANews.html#newsscan>.

September 2010 - NIDA NewsScan #68 - Research News

- PTSD contributes to teen and young adult marijuana abuse and dependence
- Identified receptor helps explain how synapses are formed
- Family-based interventions may help to prevent or reduce substance use and unsafe sexual behavior in Hispanic youth
- Identifying TRPV1 agonists may lead to new approach in developing pain relievers
- Constructive parenting behaviors improve adjustment, decrease antisocial behavior, and are commonly passed between generations
- Combining extinction therapy with pharmacotherapy holds promise in treating cocaine addiction
- Genetic variation in zebrafish advances knowledge of nicotine addiction
- Enhanced contextual memories caused by nicotine use may increase context-induced relapse

November 2010 — NIDA NewsScan #69 — Special Neuroscience Issue

- Novel local communication system in key brain reward area
- Adolescent rats may be more severely affected by prolonged nicotine exposure
- Individual impulsivity linked to natural variations in the dopamine system
- Brain regions involved in regulating craving
- Increased prediction error signals in adolescents linked to increased reward seeking
- Pre-quit reactivity to smoking-related images may signal higher risk of smoking relapse
- Novel epigenetic mechanism in the brain helps explain cocaine's addictiveness
- A striatal microRNA protects rats against compulsive cocaine-seeking
- Dopamine receptor expression dynamically changes in the rat nucleus accumbens during cocaine withdrawal

Highlights of Interviews: April - July, 2010

Discovery Magazine — Dr. Nora Volkow was interviewed about nicotine and cocaine vaccine research.

National Geographic—Dr. Nora Volkow was interviewed about how drugs work in the body.

Parade Magazine—Dr. Nora Volkow was interviewed about addiction research advances.

NBC Digital-Family Goes Strong—Dr. Geetha Subramaniam was interviewed about addiction in the family.

San Antonio Express News—Dr. Ivan Montoya was interviewed about methadone withdrawal in babies.

Bloomberg News—Dr. Ivan Montoya was interviewed about opioid addiction.

National Geographic—Drs. Susan Weiss, David McCann, and Ivan Montoya were interviewed about marijuana research.

Parents Magazine—Dr. Wilson Compton was interviewed about prescription drug abuse.

Prevention Magazine—Dr. Ruben Baler was interviewed about food addiction.

St. Petersburg Times—Dr. Marilyn Huestis was interviewed about K2/Spice.

CNN En Espanol—Dr. Nora Volkow was interviewed about fighting drug addiction in America.

Eating Well Magazine—Dr. Nora Volkow was interviewed about food addiction.

Chicago Sun-Times—Dr. Jacques Normand was interviewed about NIDA grants designed to study effective ways to prevent and treat HIV/AIDS among people in the criminal justice system.

Brain World—Dr. Joe Frascella was interviewed about how drug addiction affects the brain.

Associated Press/Bloomberg News/USA Today—Dr. Nora Volkow was interviewed about vivitrol.

Time.com—Dr. Nora Volkow was interviewed about marijuana addiction and implantable treatments for opioids.

Washington Post—Dr. Nora Volkow was interviewed about medical consequences of increased potency of marijuana.

ABC News—Dr. David Shurtleff was interviewed about DMT, a hallucinogenic drug.

National Public Radio—Dr. Phil Skolnick was interviewed about vivitrol.

ABC News online/Baltimore Sun—Dr. Liz Robertson was interviewed about drug-sniffing dogs.

Health.com—Dr. Wilson Compton was interviewed about prescription drug abuse.

Newsweek.com—Dr. Steve Gust was interviewed about the grant process for marijuana-related research.

Associated Press/San Antonio—Dr. Kevin Conway was interviewed about cocaine usage statistics.

KUSI News Channel—Dr. Gaya Dowling was part of an in-studio panel of 10 people on KUSI News Channel in San Diego, CA; for a story on "OXY: What Your Kids Aren't Telling You."

Discovery Communications—Dr. Susan Weiss and Dr. Gaya Dowling participated in a webinar (produced by Discovery Education) on marijuana and

prescription drug use for parents, teachers and students. Over 1,000 people participated. In addition, during Discovery Health's primetime show "Addiction," Dr. Redonna Chandler conducted a Facebook chat and answered questions on a variety of topics, from synthetic marijuana to issues concerning chronic pain meds.

KJZZ Radio—Dr. Cindy Miner was interviewed about National Drug Facts Week.

Multiple TV Stations—Dr. Nora Volkow was interviewed by more than 20 television stations in cities across the country about National Drug Facts Week.

'Guardian' of Prince Edward Island, Canada—Dr. Jag Khalsa, DPMCD, was interviewed.

Educational Activities

Dr. Kristopher Bough, DPMCD, participated in a science outreach program at Gettysburg College. Along with three other panelists from Temple University School of Medicine, Tenet Healthcare Corporation and the USDA, he served as a career advisor for underclass science majors. (Gettysburg, PA, Nov 6, 2010).

Upcoming Conferences/Exhibits

Community Anti-Drug Coalitions of America -- National Leadership Forum XXI

February 7-10, 2011—National Harbor, MD

American Counseling Association 2011 Annual Conference and Exposition

March 23-27, 2011—New Orleans, LA

American Psychiatric Association Annual Meeting

May 14-18, 2011—Honolulu, HI

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Planned Meetings

The National Institute on Drug Abuse (NIDA) is conducting a research track at the **American Psychiatric Association (APA) Annual Meeting** in Honolulu, Hawaii, May 14-18, 2011. NIDA will hold a number of sessions on topics unique to addiction science. Topics include: Decision Making and Addictions; Neurobiology and Treatment Implications; Does the Brain Ever Recover from Drug Addiction?; Brain Mechanisms and Neuropsychiatry in Smoking Cessation; Update on the Treatment of Comorbid Opioid Addiction and Chronic Pain; Marijuana and Psychosis: Neuroscience, Genetics and Clinical Perspectives, and; The Shrinking Psychotherapeutic Pipeline: Why has the Spigot Been Turned Off? NIDA will also lead a Forum titled, Health Reform: Transforming Addiction Services in the United States, and NIDA Director, Dr. Nora Volkow, will give an APA invited Frontiers of Science Lecture.

The National Institute on Drug Abuse (NIDA) will again sponsor the "Grant Writing Workshop" and the "Tutorials Workshop" at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting**. This year's conference will be held in Hollywood, Florida, on June 18-23, 2011. The "Tutorials Workshop" provides junior investigators with fundamental information from a variety of scientific disciplines representing the breadth of drug abuse and addiction research. The "Grant Writing Workshop" is designed to orient new research investigators to NIDA and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference. The application deadline for these travel awards is March 18, 2011.

NIDA will host its third **Mentored K Awardees Meeting**, in Rockville, MD, on July 25-26, 2011. This meeting provides a forum for NIDA mentored K awardees to:

- meet with NIDA program staff, Division Directors, and the NIDA Director and Deputy Director;
- learn strategies that will maximize their likelihood of successfully obtaining RO1 support ("grantsmanship");
- receive practical advice about transitioning to and succeeding in an independent research career;
- showcase their own current research and network with other awardees at similar points in their careers

The National Institute on Drug Abuse (NIDA) is organizing a program at the **2011 American Psychological Association (APA) Annual Meeting** in Washington, D.C., August 4-7, 2011. A number of NIDA staff throughout the Institute are involved in the planning of sessions on a wide range of topics related to addiction research. NIDA will also co-sponsor an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National

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Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

The next **National CTN Steering Committee Meetings** will be held March 15-17, 2011 in Bethesda, Maryland.

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NIDA Publications

Marijuana: Facts for Teens (Revised) — NIH Pub. No.: 10-4037

The booklet explains current knowledge about marijuana and the latest scientific information on its effects. It provides teens with questions about marijuana, including what it is, who uses it, and how it affects a person physically and mentally after short- and long-term use.

Marijuana: What Parents Need to Know (Revised) — NIH Pub. No.: 10-4036

The booklet provides valuable information from research on the dangers of marijuana. It gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about the drug.

Commonly Abused Drug Chart (Revised)

Laminated, color chart lists drugs most widely abused, their trade names and slang names, effects of intoxication, and long-term health consequences. Includes 13 Principles of Drug Abuse Treatment and graphs on drug use by students.

Principles of Drug Abuse Treatment for Criminal Justice Populations (Revised)

NIH 11-5316

Designed as a complement to NIDA's Principles of Drug Addiction Treatment: A Research-Based Guide, this booklet provides treatment principles and research findings that are of particular relevance to the criminal justice community and to treatment professional working with drug-abusing offenders.

Research Report Series: Marijuana Abuse (Spanish) — PHD948S

This Research Report summarizes what the science tells us about marijuana abuse in the United States and its effects on the brain and body. It includes an extensive review of the latest research literature presented for a general audience interested in learning more about marijuana's consequences for physical, mental, and emotional health.

NIDA Notes Article Collections on CD (Revised)

This CD-ROM contains PDF files of the 11 popular Collections of NIDA Notes articles, in addition to direct links to NIDA's Web site for current NIDA Notes articles, past and current issues of Addiction Science & Clinical Practice (formerly Science & Practice Perspectives), other NIDA publications, science summary reports, and information on drugs of abuse. The Collections include NIDA research articles on cocaine, drug abuse prevention, drugs and AIDS, drug abuse treatment, heroin, marijuana, methamphetamine, nicotine, prescription drugs, steroids, and women and sex/gender differences.

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NIDA Notes, Vol. 23, No. 3

This issue features research developing a vaccine that stimulates the body's immune system to reduce cocaine abuse. It also includes an article documenting the effectiveness of methadone maintenance programs in therapeutic communities. Another article explores the link between regular marijuana use and a dangerous form of testicular cancer. On the clinical front, the issue examines the long-term effectiveness of Multidimensional Family Therapy for adolescent drug abusers. The NIDA at Work section focuses on the Neuroscience Consortium, which monitors developments in brain science to ensure that NIDA's research programs are infused with the most advanced knowledge and tools. In the Director's Perspective, Dr. Nora D. Volkow describes the benefits of incorporating motivational incentives into substance abuse treatment to encourage drug abstinence and reinforce healthy behaviors.

NIDA Notes, Vol. 23, No. 4

This issue features an article on the more than 1,000 proteins in the neurons of the brain's reward system that may be altered by chronic cocaine abuse, contributing to the transition from voluntary to compulsive drug taking. Another feature on recent NIDA-funded animal research indicates that drugs of abuse may diminish production of new hippocampal neurons in adults, thereby increasing vulnerability to drug addiction. Another article, evaluating five smoking cessation programs, found that a combination of nicotine patch and lozenge offered the best results. An additional feature indicates that Communities That Care, a program that implements evidenced-based, substance abuse prevention programs, helped students reduce delinquency, initiation of alcohol and tobacco use, and binge drinking. Another article reports that aiding HIV-infected prisoners with the paperwork necessary to obtain free antiretroviral therapy after release substantially reduced treatment interruptions. Finally, in the Director's Perspective, D Nora D. Volkow outlines the Institute's commitment to research that addresses the potential for physical activity to prevent substance abuse.

NIDA Notes, Vol. 23, No. 5

This issue of NIDA Notes reports that in children exposed to prenatal maternal smoking, the gene variant associated with higher risk of developing a conduct disorder is different for boys than for girls. Another feature indicates that gender-specific, multi-session programs designed to teach safe-sex behaviors are effective in reducing unprotected sex among patients receiving drug abuse treatment. Another article presents research indicating that state and federal prison systems underutilize opioid replacement therapy, an evidence-based treatment for opioid addiction. This issue also reports on a neuropeptide blocker that dampens rats' motivation for cocaine and rich food; the finding may introduce a new strategy for treating both drug addiction and obesity. Finally, in this month's Director's Perspective, Dr. Nora D. Volkow discusses NIDA's effort to develop treatments for groups with the highest smoking rates, including high school dropouts, Native Americans, and people with psychiatric disorders.

NIDA in the News

- Issue #31 of *NIDA in the News* was distributed to all NIDA HQ, IRP and contractor staff on September 14, 2010.
- Issue #32 of *NIDA in the News* was produced and sent out on November 12, 2010.

CTN-Related Publications

Six editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the

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CTN and NIDA.

Data from 23 CTN studies are now available on the CTN Data Sharing Web Site <http://www.nida.nih.gov/CTN/Data.html>. Over 300 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

International Program-Related Publications

NIDA International Program E-News

- *September 2010* - This issue featured NIDA activities at the International AIDS Meeting, including the new International AIDS Society-NIDA Fellows and the UNAIDS Red Ribbon Award presented to the Palestinian Substance Abuse Research Center, which has long been active in IP programs and international collaborative research on drug use and HIV/AIDS. The issue also reported on the 2010 NIDA International Forum and the International Awards of Excellence presented to NIDA grantees Dr. Walter Ling, University of California Los Angeles; Dr. Evgeny Krupitsky, Pavlov Medical University, St. Petersburg, Russia; Dr. Thomas F. Babor, University of Connecticut; and Dr. Robin Room, University of Melbourne (Australia).
- *November 2010* - This issue reported on IP-supported regional meetings held in Penang, Malaysia; Oslo, Norway; and Kiev, Ukraine, to build regional collaboration on drug abuse research. Other features included the Prague Declaration on Drug Policies, organized by two former NIDA Humphrey Fellows; IP support for international researchers at the National Hispanic Science Network meeting; and the 2010 International Conference on Women, Children, and Gender.

Other Publications

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Director's Report to the National Advisory Council on Drug Abuse - February, 2011

Staff Highlights

Staff Honors

Dr. Jennifer Bossert, IRP, received a travel award from the American College of Neuropsychopharmacology. She was invited to present at their 49th Annual Meeting, December 5-9, 2010, in Miami Beach, FL. Her poster was entitled "Selectively activated neurons on ventral medial prefrontal cortex mediate context-induced reinstatement of heroin seeking."

Dr. Satoshi Ikemoto, IRP, received the Brain Research Award from Elsevier for his review article, which received the most citations during 2009 from articles published in Brain Research Reviews during 2007 and 2008.

Dr. Satoshi Ikemoto was promoted to Senior Investigator and Chief, Neurocircuitry of Motivation Section, IRP.

Dr. Aleta Meyer, Prevention Research Branch, DESPR, was honored with a Servant Leader Award by the Association for Experiential Education at their annual meeting in Las Vegas, NV, on November 5, 2010. She was recognized for her active leadership and commitment in encouraging research on the impact of adventure and experiential approaches for the prevention of drug use and the promotion of positive youth development.

Dr. Nadine Rogers, OEA, was accepted into Cohort 13 of the International Experience and Technical Assistance (IETA) program, a developmental training program for Federal public health employees offered by the Center for Global Health, at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Dr. Rogers is one of seven (7) employees selected from across the U.S. Department of Health & Human Services to participate in the program in 2011.

Dr. Toni Shippenberg, Chief, Integrative Neuroscience Branch, was appointed co-chair of the Publications Committee of the American College of Neuropsychopharmacology.

Dr. Toni Shippenberg received the NIDA/NIAAA Women Scientist Advisors 2010 Achievement Award in recognition of her excellence in research and mentoring.

Dr. Florence Theberge and **Danielle Guez-Barber** from the Neurobiology of Relapse Section, IRP, received a Fellows Award for Research Excellence (FARE) on October 22, 2010. Their submissions were selected from the top 25% of abstracts submitted from 50 different study sections.

Danielle Guez-Barber, IRP, used her FARE Award to present a poster at the American College of Neuropsychopharmacology 49th Annual Meeting,

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December 5-9, 2010, Miami Beach, FL. The title of her poster was "FACS Identifies Unique Gene Regulation in Adult Striatal Neuronal Ensembles Selectively Activated During Cocaine-induced Behavior."

Ms. Fiori Vollrath-Smith, IRP, received the Julius Axelrod Travel Award for her poster presented at the 2010 Society for Neuroscience meeting.

Staff Changes

Dr. David Shurtleff, Director of NIDA's Division of Basic Neuroscience and Behavioral Research, (DBNBR), was selected to serve as ***NIDA's Acting Deputy Director***, effective January 15, 2011. David received his B.S. degree from the University of Massachusetts, Amherst and his Ph.D. in Experimental Psychology from The American University, Washington DC. Prior to his tenure at NIDA, he was a Research Fellow at the Walter Reed Army Institute of Research, in the Department of Medical Neurosciences and a Research Psychologist at the Naval Medical Research Institute in Bethesda MD. Before becoming Director of DBNBR, David served as the Deputy Director for the Division and as a Health Scientist Administrator where he managed a research portfolio in the basic behavioral sciences, including research in the cognitive sciences, behavioral economics, decision theory, and human and animal models of impulsivity, risk taking and other aspects of drug addiction. In 2007, he received the NIH Director's Award for outstanding contributions to the development and advancement of diverse programs in basic neuroscience and behavioral research. Dr. Shurtleff is a Fellow of the American Psychological Association's Division 28, Psychopharmacology and Substance Abuse, and Division 6, Behavioral Neuroscience and Comparative Psychology.

Dr. Joni Rutter, Associate Director for Population and Applied Genetics, Division of Basic Neurosciences and Behavioral Research has been named ***Acting Director, Division of Basic Neuroscience and Behavioral Research***. Joni earned a Ph.D. in Pharmacology and Toxicology from Dartmouth Medical School in 1999 and joined the NIH that same year as a post-doctoral fellow in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute. She moved to NIDA in 2003 as a program director in the Genetics and Molecular Neurobiology Research Branch where she continues to have a human genetics portfolio. Dr. Rutter has been actively involved in oversight and the continued development of genomics research at NIDA, which includes the NIDA Center for Genetic Studies repository of clinical data and biologic samples for drug abuse research in genetics. She has also been involved with several trans-NIH programs, including Roadmap, (Epigenetics, Interdisciplinary Research Consortia) as well as the NIH Genes, Environment, and Health Initiative.

Dr. Lucinda Miner, Deputy Director of NIDA's Office of Science Policy and Communications (OSPC) left NIDA in mid January to assume the position of Associate Director for Communications with the FDA's Office of Science in their new Center for Tobacco Products. Cindy began her career at NIDA in 1992 as a Senior Staff Fellow at IRP's Preclinical Pharmacology Branch and became Acting Chief of the Molecular Genetics Section a year later. In 1996 she joined the Office of Science Policy and Communications. For nearly 20 years she has contributed to NIDA's growth with contributions to science planning, policy, congressional, and communications activities, research training and science education programs.

Dr. Susan R.B. Weiss, Chief of OSPC's Science Policy Branch has been named ***Acting Director, Office of Science Policy and Communications***. Susan has been with NIDA for more than 8 years and continues to provide excellent leadership and quality control for our diverse communications projects and training programs. Before coming to NIDA, Susan was the Senior Director of Research at the National Mental Health Association (now Mental Health

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America), and Unit Chief, Behavioral Biology Research program at the National Institute of Mental Health (NIMH), where her research efforts focused on developing treatments to address the evolving nature of psychiatric and neurologic illnesses. Susan earned her Ph.D. from the University of Maryland and her B.S. in Psychology from the State University of New York at Stony Brook.

Dr. Gaya J. Dowling, Deputy Chief of OSPC's Science Policy Branch has been named ***Acting Chief of the Science Policy Branch, OSPC***. During Gaya's tenure at NIDA, she has helped to educate a variety of audiences about the science of drug abuse and addiction—developing, guiding, and targeting communications for many different audiences, including Congress, the White House Office of National Drug Control Policy, other Federal Agencies, constituency organizations, physicians, and the general public. Gaya earned her Ph.D. in Neurobiology at the University of California, Davis and subsequently worked at both the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke.

Dr. Amy Newman has been selected as ***Deputy Scientific Director at NIDA's Intramural Research Program (IRP)***. She is also Chief of the IRP's Medicinal Chemistry Section. Dr. Newman received her Ph.D. in medicinal chemistry from Virginia Commonwealth University.

Dr. Roy Wise has stepped down as ***Chief of the IRP's Behavioral Neuroscience Branch***, devoting himself, after 14 years as Branch Chief and 10 as Deputy Director of the IRP, to what Julius Axelrod described at the best job at NIH: Section Chief. Prior to coming to the NIDA IRP, he taught at Concordia University in Montreal, where he was Professor of Psychology and founding director of the Center for Studies in Behavioral Neurobiology.

Dr. Yavin Shaham has been selected to take on the role of ***Chief, Behavioral Neuroscience Branch, IRP***. He received his Ph.D. in 1992 from the Uniformed Services University of the Health Sciences, Bethesda MD. His postdoctoral training from 1992 to 1995 was at Concordia University, Montreal, and from 1996 to 1998, he was an investigator at the Addiction Research Center in Toronto. He joined the NIDA intramural program in 1998 as a tenure-track investigator. In 2003, he received tenure at NIH and became a Section Chief of the Neurobiology of Relapse Section.

Dr. Toni S. Shippenberg was appointed ***Chief*** of the newly created ***Integrative Neuroscience Branch*** of the NIDA IRP. The branch consists of the Integrative Neuroscience Section, Molecular Pathobiology Section, Structural Biology Unit and the NIDA IRP multiphoton and stereology CORE facility.

Dr. Sheri Grabus joined the OSPC in November 2010 as the ***NIDA Deputy Press Officer***. Prior to joining NIDA, Sheri was trained as a neuroscientist and has a Ph.D. from American University in Psychopharmacology and Neuroscience. As a postdoc at Virginia Commonwealth University she designed mouse models of nicotine dependence and reward, and studied nicotinic agonists and antagonists, including bupropion. She has also taught at the college level—including courses in psychology, substance abuse prevention and treatment, and she has lectured on drug dependence, pharmacology and drugs and pain control.

Barbara E. Moquin, PhD, APRN, BC-P, has joined the ***CCTN*** office as a ***Health Science Administrator*** through a one year detail. Dr. Moquin has worked extensively with the military, and will lead an effort to explore potential collaboration with the Veterans Administration on research areas such as PTSD-SUD. Dr. Moquin will assist with NIDA representation at the National Center for Research Resources and Clinical and Translational Science Awards (CTSA) research network committees regarding Community Engagement and

Education. Dr. Moquin will also be engaged in a range of other projects and activities during her time with CCTN. Dr. Moquin completed a BSN at Georgetown University, an MSN in Psychiatric/Mental Health at the Catholic University of America and a PhD in Transpersonal Psychology at Howard University. Her trainings include the Harvard Mind-Body Institute in Behavioral Medicine amongst others. She is nationally Board-Certified as an Advanced Practice Nurse /Psychotherapist and as a Health Promotion Director, with expertise in Stress Neuroscience and Management, Sleep, Health Equity, Suicide Prevention and Substance Abuse.

Yvonne Moskal joined the **Financial Management Branch (FMB)** in the Office of Management (OM) as our newest **Budget Analyst** on January 18, 2011. Yvonne comes to NIDA from the Substance Abuse and Mental Health Services Administration (SAMHSA) where she worked as a Budget Analyst and she has prior budget experience working with both FEMA and the NIH Office of Budget.

Dr. Elena Schifirnet joined the **IRP's Behavioral Neuroscience Research Branch** as a **Visiting Fellow**.

Elizabeth Ginexi, Ph.D. of the Prevention Research Branch, DESPR, has accepted a position as a Program Director in the Tobacco Control Research Branch in the Behavioral Research Program of the Division of Cancer Control and Population Sciences at NCI.

Aleta Meyer, Ph.D. of the Prevention Research Branch, DESPR, has accepted a position as a Social Science Research Analyst in the Division of Child and Family Development, at the Office of Planning, Research, and Evaluation Administration for Children and Families.

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Grantee Honors

NIDA grantee **Sabina S. Alistar**, a doctoral student from the Management Science and Engineering Department at Stanford University, was awarded First Prize in the Lee B. Lusted Student Competition for Outstanding Presentation of Research at the 32nd Annual Meeting of the Society for Medical Decision Making, October 23-27, 2010, Toronto, Canada. Her presentation was on "A Practical Tool for Allocating Funds for HIV Prevention and Treatment Scale Up," and resulted from research she conducted with Drs. Margaret Brandeau of Stanford University and Eduard J. Beck of the UNAIDS.

NIDA grantee **Dr. Robert Booth**, of the University of Colorado at Denver, received the Award for Excellence in Global Health from the University's Center for Global Health on October 16th. This award recognized Dr. Booth for his dedication to public health, including his pioneering work in the HIV testing and counseling using a manually-driven model that is easy to implement, inexpensive, and readily accepted by drug injectors—a model that may soon be adopted by the Global AIDS Fund.

Dr. Kathleen T. Brady, Principal Investigator of the CTN Southern Consortium Node, has received this year's American Academy of Addiction Psychiatry (AAAP) Founders' Award, which is presented each year to an "outstanding member of the community whose work in the field of addiction has contributed significantly to the science, teaching, treatment, and public policy in the addictions." Dr. Brady received the award at the Academy's Annual Meeting held December 2-5, 2010 in Boca Raton, FL.

Mauricio R. Delgado, Ph.D., a Principal Investigator at Rutgers University, was selected as one of 85 recipients of the Presidential Early Career Awards for Scientists and Engineers (PECASE).

NIDA grantee **Dr. Sam Friedman**, of the National Development Research Institute (NDRI), New York, N.Y., received the 2010 Senior Scholar Award of the Alcohol, Drugs, and Tobacco Section of the American Sociological Association.

Dr. Douglas Heckathorn, Professor of Sociology at Cornell University, received a citation award from Thomson Reuters in September 2010 for his article ("Extensions of Respondent-Driven Sampling: Analyzing continuous variables and controlling for differential recruitment") published in 2007 in *Sociological Methodology*. This award recognizes authors across 22 disciplines for scientific papers that are cited among the top one-tenth of one percent (0.1%) in a current bimonthly period. Dr. Heckathorn's work with RDS grew out of NIDA-funded research.

Santosh Kumar, Ph.D., University of Memphis, was selected by Popular Science as one of this year's "10 Brilliant Scientists" for development of

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"AutoSense [which] uses a chest band and an armband to track respiration, heart rate and blood pressure, and features an activity monitor É to reveal when an addict in treatment, for instance, is É smoking [and] can identify stress and self-destructive behavior and anticipate when the addict is about to relapse, alerting him—or his therapist—to his increased susceptibility."

NIDA grantee **Douglas K. Owens**, of the VA Palo Alto Health Care System and the Department of Medicine at Stanford University, was awarded the John Eisenberg Award in Recognition of Exemplary Leadership in the Practical Application of Medical Decision Making Research at the 32nd Annual Meeting of the Society for Medical Decision Making, October 23-27, 2010, Toronto, Canada. This award recognized Dr. Owens' contributions to medical decision making, including its use in shaping current policies on HIV prevention and treatment. In particular, Dr. Owens' work on the expansion of HIV screening has had a seminal impact in the development of US guidelines on HIV screening and in support of strategies to increase HIV testing, treatment, and care for HIV-positive individuals in the US and in international locations.

Tamara Phillips, Ph.D. (PI of a Component of P50 DA18165) received the 2010 Distinguished Scientist Award from the International Behavioural and Neural Genetics Society and presented a talk at their annual meeting on 15 May 2010 in Halifax, Nova Scotia, Canada. Her talk was entitled, "Cool! I can breed for this!," and she gave highlights of her more than 30 years of research using selectively bred lines to study the genetics of addiction related traits.

Dr. José Szapocznik, Principal Investigator of the CTN Florida Node Alliance, was awarded the National Hispanic Science Network (NHSN) Tribute Award to honor his leadership and contributions to the NHSN over the last ten years and was also recently appointed as the new executive dean for research at the Miller School of Medicine.

In Oviedo, Spain on October 22, 2010, NIDA grantee **Dr. Linda Watkins** (University of Colorado) along with NIH grantee **Dr. David Julius** (University of California) and **Dr. Baruch Minke** (Hebrew University of Jerusalem) received the 2010 Prince of Asturias Award for Technical and Scientific Research by the Prince of Asturias Foundation. This prestigious award was given based on the significant advances these individuals have made in the development of novel approaches to the treatment of pain.

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